DRUGS

DRUGS IN NEUROLOGY

Edited by Sathiji K. Nageshwaran
David Ledingham | Heather C. Wilson

Covers the breadth of medications used in modern neurology, with a clinical focus

Updated to mirror the significant progress made in each field of Neurology

Includes practical aspects related to prescribing and therapeutic drug monitoring

Based on the most up-to-date evidence based guidance

SECOND EDITION • SECOND EDITION •
2

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Drugs in Neurology

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SECOND EDITION

EDITED BY

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Foreword

This incisively written second edition guide to drugs used in neurologic therapeutics is a welcome addition and update. It differs from similar texts in that chapters are written cooperatively between UK and American authors who are academic experts in their fields. This gives a broad perspective and style that is not to be found elsewhere. Further welcome is the concision of writing, summarizing the disorders being discussed with very updated comments and figures, followed by a no-nonsense and balanced guide to treatment of conditions such as epilepsy, dementia, cerebrovascular disease, and all other major categories of disease, including three chapters at the end that are well done and provocative on uro-neurology, drugs causing neurological disease, and neurogenetics. I see this book as a quite valuable aid to clinical practice but also as an excellent basis for study for students, registrars, and residents seeking to review their knowledge. It will be wonderful to have on my own bookshelf.

Dr. Allan Ropper
Prof. of Neurology, Harvard Medical School

Preface

Since the publication of the first edition of *Drugs in Neurology*, a revolution in the Neurological sciences has been underway with numerous previously untreatable conditions, receiving disease modifying treatment allocations due to the tireless efforts of researchers, clinicians, and patient advocacy groups.

Following on from the first edition, *Drugs in Neurology* second edition is completely updated, with a new chapter on Neurogenetics. We comprehensively cover the modern management of adult neurological diseases. Emphasis is placed on the pharmacological underpinnings behind the drugs used and on the evidence-base for their use, but respect is also given to treatment recommendations established as a result of decades of clinical experience from experts in the field.

We hope this book will be of value to trainees in neurology and clinical pharmacology and to all those involved in the treatment of adults with neurological disorders.

We welcome comments and feedback from readers. Please email all correspondence to: editors.drugsinneurology@gmail.com.

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Abbreviations

#NNT	Number needed to treat
AAR	Annualized attack rate
AAV	Adeno-associated virus
ACE	Angiotensin-converting enzyme
ACRA	Acetylcholine receptor antibody
ACT	Activated clotting time
AD	Alzheimer's disease
AD	Autosomal dominant
ADA	Anti-drug antibodies
ADH	Antidiuretic hormone
ADHD	Attention-deficit/hyperactivity disorder
ADWP	Autoimmune Diseases Working Party
AECA	Anti-endothelial cell antibodies
AED	Automated external defibrillators
AF	Atrial fibrillation
AGEP	Acute generalized exanthematous pustulosis
AHA	American Heart Association
AHP	Acute hepatic porphyrias
AHSCT	Autologous haematopoietic stem cell therapy
AIDP	Acute inflammatory demyelinating polyradiculopathy
AIMS	Abnormal involuntary movements score
AIP	Acute intermittent porphyria
ALA	Aminolevulinic acid
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
AMAN	Acute motor axonal neuropathy
AMSAN	Acute mixed sensory and motor neuropathy
ANA	Antinuclear antibodies
AR	Autosomal recessive
ARB	Angiotensin receptor blocker
ARE	Antioxidant response element
ARIA	Amyloid-related imaging abnormalities
ARR	Absolute risk reduction
ARR	Annual relapse rate
ARR	Annualized relapse rate
ASA	American Stroke Association
ASM	Anti-seizure medication
ASS	Anti-synthetase syndrome
ATACH	Antihypertensive Treatment of Acute Cerebral Hemorrhage
AWH	Arteriolar wall hyper-fluorescence
BD	Behçet's disease
BDI	Beck Depression Inventory
BMD	Becker muscular dystrophy
BP	Blood pressure
BPPV	Benign paroxysmal positional vertigo
BRAO	Branch retinal artery occlusion
BSA	Body surface area
CAA	Cerebral amyloid angiopathy
CAFA	Canadian Atrial Fibrillation Anticoagulation
CARE	Cholesterol and Recurrent Events
CAST	Chinese Acute Stroke Trial
CBT	Cognitive behavioural therapy
CBTRUS	Central Brain Tumor Registry of the United States
CCB	Calcium channel blockers
CDP	Confirmed disability progression
CGRP	Calcitonin gene-related peptide
CHD	Coronary heart disease
CHHIPS	Controlling hypertension and hypotension immediately post-stroke
CHM	Commission on human medicines
CIDP	Chronic inflammatory demyelinating polyneuropathy
CK	Creatine kinase
CLIPPERS	Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids

CMAP	Compound muscle action potentials
CMS	Congenital myasthenic syndromes
CNS	Central nervous system
COC	Combined oral contraceptives
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CVA	Cerebrovascular accident
CVST	Cerebral venous sinus thrombosis
CXR	Chest X-ray
DA	Dopamine agonists
DADS	Distal acquired demyelinating symmetric
DAPT	Dual antiplatelet therapy
DATATOP	Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism
DAWS	Dopamine agonist withdrawal syndrome
DBS	Deep brain stimulation
DDI	Dopa decarboxylase inhibitor
DEXA	Dual-energy X-ray absorptiometry
DLB	Dementia with Lewy bodies
DMD	Duchenne and Becker muscular dystrophy
DMD	Duchenne's muscular dystrophy
DML	Distal motor latency
DMT	Disease-modifying therapy
DORA	Dual orexin receptor antagonist
DRD	Dopa-responsive dystonia
DRESS	Drug rash with eosinophilia and systemic symptoms
DWI	Diffusion-weighted imaging
EAFT	European Atrial Fibrillation Trial
ECT	Ecarin clotting time
EDSS	Expanded Disability Status Scale
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
ER	Endoplasmic reticulum
ERT	Enzyme replacement therapy
ESETT	Established status epilepticus treatment trial
ET	Essential tremor
EU	European Union
FA	Friedreich's ataxia
FBC	Full blood count
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FLAIR	Fluid-attenuated inversion recovery
FTD	Frontotemporal dementia
FVC	Forced vital capacity
GA	General anaesthetic, *or* Glatiramer acetate
GBS	Guillain–Barre syndrome
GCA	Giant cell arteritis
GD	Gaucher's disease
GDS	Geriatric Depression Scale
GON	Greater occipital nerve
HAART	Highly active antiretroviral therapy
HC	Hemicrania continua
HD	Huntington's disease
HDL	High-density lipoprotein
HIT	Heparin-induced thrombocytopenia
HSP	Hereditary spastic paraplegia
HSV	Herpes simplex virus
HUS	Haemolytic uraemic syndrome
IA	Intra-arterial
IAR	Infusion-associated reactions
IASP	International Association for the Study of Pain
IBM	Inclusion body myositis
ICD	Impulse control disorders
ICH	Intracerebral haemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
IHS	International Headache Society
IIH	Idiopathic intracranial hypertension
IIM	Idiopathic inflammatory myopathies
ILAE	International League Against Epilepsy
ILD	Interstitial lung disease
IMNM	Immune-mediated necrotizing myopathy
IQ	Intelligence quotient

IRIS	Immune reconstitution inflammatory syndrome
IRLS	International Restless Legs Scale
ISC	Intermittent self-catheterization
IST	International Stroke Trial
ITP	Immune thrombocytopenic purpura
LDL	Low-density lipoprotein
LETM	Longitudinally extensive transverse myelitis
LID	Levodopa-induced dyskinesias
LMWH	Low-molecular-weight heparin
LO	Lorenzo's oil
LOTS	Late-Onset Treatment Study
LP	Lumbar puncture
LPS	Latency to persistent sleep
LS	Least squares
LSD	Lysosomal storage disorders
LVO	Large vessel occlusion
MAG	Myelin-associated glycoprotein
MAM	Menstruation-associated migraine
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MDS	Movement Disorder Society
MG	Myasthenia gravis
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MICON	Microbleeds International Collaborative Network
MIMS	Mitoxantrone in Multiple Sclerosis Study
MISTIE	Minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation
MMN	Multifocal motor neuropathy
MMSE	Mini mental state examination
MND	Motor neuron disease
MOGAD	MOG antibody disease
MOH	Medication overuse headache
MPA	Mycophenolic acid
MR	Magnetic resonance
MRS	Modified Rankin Scale
MS	Multiple sclerosis
MSA	Multiple system atrophy
MSCRG	Multiple Sclerosis Collaborative Research Group
MTIC	Monomethyl triazeno imidazole carboxamide
MWT	Maintenance of wakefulness test
NEDA	No evidence of disease activity
NfL	Neurofilament light
NIHSS	National Institutes of Health Stroke Scale
NMOSD	NMO spectrum disorder
NMS	Neuroleptic malignant syndrome
NMS	Neuroleptic malignant syndrome
NREM	Non-rapid eye movement
NSAID	Non-steroidal anti-inflammatory drugs
OAB	Overactive bladder
OMS	Opsoclonus-myoclonus syndrome
ONTT	Optic Neuritis Treatment Trial
ORF	Open reading frame
OSA	Obstructive sleep apnoea
PAN	Prominent in cryoglobulinaemia and polyarteritis nodosa
PCC	Prothrombin complex concentrate
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PE	Phenytoin equivalents
PE	Phenytoin sodium, USP equivalents
PED	Paroxysmal exercise induced dyskinesias
PEMA	Phenyl-ethyl malonamide
PERM	Progressive encephalomyelopathy with rigidity and myoclonus
PET	Positron emission tomography
PFO	Patent foramen ovale
PH	Paroxysmal hemicrania
PHS	Parkinson's hyperpyrexia syndrome
PLEX	Plasma exchange
PLMD	Periodic limb movement disorder

PLMS	Periodic limb movements of sleep
PML	Progressive multifocal leukoencephalopathy
PNES	Psychogenic non-epileptic seizures
PNS	Peripheral nervous system
POEMS	Polyneuropathy, organomegaly, endocrinopathy, M-protein spike, and skin manifestations
PR	Per rectum
PRES	Posterior reversible encephalopathy syndrome
PROMM	Proximal myotonic myopath
PSP	Progressive supranuclear palsy
PTNS	Percutaneous or transcutaneous tibial nerve stimulation
QMG	Quantitative Myasthenia Gravis
RBD	REM sleep behaviour disorder
RCT	Randomized controlled trial
RCVS	Reversible cerebral vasoconstriction syndrome
RDA	Recommended dietary allowance
REGARD	REbif vs Glatiramer Acetate in Relapsing MS Disease
REM	Rapid eye movement
REMS	Risk evaluation mitigation strategy
RLS	Restless legs syndrome
ROPE	Risk of paradoxical embolism
RP	Relapsing polychondritis
RRMS	Relapsing-remitting multiple sclerosis
SAH	Subarachnoid haemorrhage
SANAD	Standard And New Antiepileptic Drugs
SBMA	Spinal and bulbar muscular atrophy
SCA	Spinocerebellar ataxia
SCI	Spinal cord injury
SCLC	Small cell lung cancer
SGA	Small for gestational age
SGI	Subject Global Impression
SIADH	Syndrome of inappropriate antidiuretic hormone
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic lupus erythematosus
SMA	Spinal muscular atrophy
SMD	Standardized mean difference
SMS	Spinal magnetic stimulation
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SRT	Stereotactic radiosurgical techniques *or* Substrate replacement therapy
SSRI	Selective serotonin reuptake inhibitors
SUDEP	Sudden unexpected death in epilepsy
SUNCT	Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing
SWI	Susceptibility-weighted images
TAC	Trigeminal autonomic cephalalgias
TFT	Thyroid function tests
TIA	Transient ischaemic attack
TICI	Thrombolysis in cerebral infarction
TM	Transverse myelitis
TOP	Tysabri Observational Program
TRAP	Tartrate-resistant acid phosphatase
TS	Tourette's syndrome
TT	Thrombin time
TTH	Tension-type headache
TTP	Thrombotic thrombocytopenic purpura
U&E	Urea and electrolytes
UHDRS	Unified Huntington's Disease Rating Scale
ULN	Upper limit of normal
UMN	Upper motor neuron
UPDRS	Unified Parkinson's Disease Rating Scale
UPR	Unfolded protein response
VAMP	Vesicle-associated membrane protein
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VGCC	Voltage-gated calcium channels
VITT	Vaccine-induced thrombosis and thrombocytopenia
VLCFA	Very-long-chain fatty acids

VOR	Vestibulo-ocular reflex
VZV	Varicella-zoster virus
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WASO	Wake time after sleep onset
WBC	White blood cells
WCC	White cell count
WD	Wilson's disease
WHO	World Health Organization
WMD	Weighted mean difference
YGTSS	Yale Global Tic Severity Scale

Section 1

Neurological conditions

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Chapter 1

Headache

Introduction *4*
Headaches *4*

Introduction

Headache is one of the most common neurological presentations to primary care and neurology clinics. It accounts for approximately 5% of primary care visits and 2% of emergency department visits. Headache disorders were cited as the third highest cause of global disability amongst all ages and genders in the most recent Global Burden of Disease study.[1]

Classification

The International Headache Society (IHS) classification for headache (ICHD-3) divides headache disorders into primary headache syndromes, secondary headache syndromes, and painful lesions of the cranial nerves and other facial pain.[2] Primary headache disorders include migraine, tension-type headache (TTH), and trigeminal autonomic cephalalgias (TACs). Secondary headache disorders are conditions in which headache arises due to an underlying identifiable cause. Medication overuse headache (MOH) is the most commonly encountered secondary headache in clinical practice.

Headaches

- Primary headache syndromes include:

1. Migraine with and without aura.
2. TTH.
3. TACs, e.g. cluster headache, paroxysmal hemicrania (PH), hemicrania continua (HC), SUNCT* and SUNA**.
4. Other primary headaches—primary cough, exertional, stabbing and thunderclap headaches, and headaches associated with sexual activity.
   * short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.
   ** short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.

- Secondary headache syndromes include:

1. Headaches secondary to head and neck pathology.
2. Substance use or its withdrawal, e.g. MOH.
3. Psychiatric disorder.

- Cranial neuralgias and facial pain, e.g. trigeminal neuralgia.

This chapter will discuss the symptomatic treatment of primary headache syndromes, idiopathic intracranial hypertension (IIH), and MOH. Trigeminal neuralgia is discussed in Chapter 5 , Neuropathic pain.

General principles of treatment

1. *Headache diaries and regular review*: patients should be encouraged to keep headache diaries in order to identify associations with previously unknown triggers and to assess medication efficacy. They should be regularly reviewed to monitor efficacy of treatment and side effects of drugs used.
2. *Acute treatment of headache attacks*: treatment should be initiated as early as possible in the attack. The analgesic agents used should be proportional to the severity of the headache and be effective and acceptable to the patient.

3. *Prevention of headache attacks*: preventative treatment should be initiated in consultation with the patient. This is typically started when quality of life is impaired, e.g. headache frequency is >2 attacks per month, there is severe or prolonged aura, or acute treatment is ineffective. The agent used depends upon patient choice, comorbidities, and the risk of drug interactions. Treatment should be started with a proposed duration in mind, typically 3–6 months.
4. *Mini-prophylaxis/pre-emptive treatment*: patients with specific predictable triggers for headache, e.g. menstruation-associated migraine (MAM) or exercise-induced migraine, may benefit from mini-prophylaxis taken prior to the trigger, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) or triptans.
5. *Avoidance of MOH* (see Medication overuse headache, p. 14): most acute abortive headache treatments are associated with MOH.

Primary headache

The American Headache Society (AHS)/American Academy of Neurology (AAN), European Federation of Neurological Societies (EFNS), and National Institute for Health and Care Excellence (NICE) in the UK[3] have outlined recommendations for the management of common headache disorders. The following pages will focus on the primary headaches and selected secondary headaches; IIH and MOH, as these are the most commonly encountered.

Migraine with or without aura

Migraine is a common headache disorder, with an estimated 1 billion people affected worldwide.[1] It affects 18% of women and 5% of men in developed countries. In adults, it is typically unilateral but can be bilateral. It is moderate to severe in intensity, evolves over minutes to hours, and is described as pulsating or throbbing. It can be associated with photophobia, phonophobia, nausea, and vomiting. Aura, a constellation of focal neurological symptoms, typically visual, sensory, or motor, if present, usually precedes the onset of headache but may occur during or after the headache attack.

Acute treatment of episodic migraine

An individualized approach is required when choosing the right agent considering the patient's characteristics (e.g. age, co-morbid conditions). A number of newer agents have also recently been made available and might come to be used as a first, second-, or third-line treatment depending on clinician experience and cost.

- *First line*: aspirin 600–900 mg, NSAID (ibuprofen 400–600 mg, diclofenac 50 mg), or paracetamol/ acetaminophen 1 g.
- *Second line*: oral triptan (sumatriptan 50–100 mg, zolmitriptan 2.5–5 mg, almotriptan 12.5 mg, eletriptan 20–80 mg).

- *Third line*: non-oral triptan (sumatriptan 6 mg subcut, 10–20 mg intranasal, zolmitriptan 5 mg intranasal) or combination therapy.
- If treatment fails with the above, ergot alkaloids may be used.
- *Drugs to avoid*: opioids.
- *Adjuncts*: prokinetic agents, e.g. metoclopramide 10 mg or domperidone 10 mg, can be given if there is nausea/vomiting or suspicion of significant absorption delay due to gastric stasis.
- *Newer agents*: small molecule calcitonin gene-related peptide (CGRP) antagonists (rimegepant, ubrogepant and zavegepant), 5-HT1F receptor agonist (lasmiditan).

Evidence base

(For comparisons, see Triptans monograph, p. 471.)

High-quality evidence exists for the efficacy for triptans and NSAIDs for the acute treatment of episodic migraine, both alone and in combination. Additionally, high-quality evidence exists for acetaminophen, dihydroergotamine, CGRP antagonists, and lasmiditan. There is limited evidence to support the use of opioids.

A large meta-analysis (66 trials) of oral triptans in migraine treatment found that almotriptan (12.5 mg), eletriptan (80 mg), and rizatriptan (10 mg) were more effective and consistent than sumatriptan in reducing headache severity, but that eletriptan at this dose was less well tolerated; 59% of patients had a significant improvement in headache at 2 h with sumatriptan 100 mg.[4] In a meta-analysis (16 trials) of metoclopramide in acute migraine, IV metoclopramide was found to be more effective than placebo at reducing headache severity.[5] There are no combined studies comparing different NSAIDs in migraine, but each individual NSAID has been shown to be superior to placebo in reducing headache severity in randomized controlled trials (RCTs). Paracetamol 1 g has been shown to be effective in reducing headache pain and the symptoms of photophobia and phonophobia, compared with placebo, with about 58% of patients responding to paracetamol. Ergot alkaloids (dihydroergotamine and ergotamine) are less effective than triptans. There is some RCT evidence showing efficacy for ergotamines, but their use is limited by side effects. They may have a role in patients with prolonged migraine and a high rate of headache recurrence.

RCTs have demonstrated efficacy of rimegepant[6] and ubrogepant[7] in the treatment of acute migraine. Rimegepant 75 mg resulted in 19.6% reduction at 2 h compared to 12% in the placebo group (CI: 3.3 to 11.9; $p < 0.001$). Ubrogepant 100 mg and 50 mg resulted in freedom from pain in 21.2% ($p < 0.001$) and 19.2% ($p = 0.002$), respectively, compared with 11.8% in the placebo group.

RCTs have shown the efficacy of lasmiditan in the treatment of acute migraine. The overall effect estimate in a meta-analysis of four RCTs[8] showed that lasmiditan was significantly superior to placebo in terms of pain-free (RR 1.71), pain relief (RR 1.40), global impression (very much/much better) (RR 1.55), and no/mild disability (RR 1.15) at 2 h.

Recommendations

1. Simple analgesics, e.g. paracetamol or NSAIDs may be used for acute migraine if they are effective. If there is failure of response with one, an alternative can be used but risk of MOH should be considered.
2. The most cost-effective triptan should be chosen first. If there is no response, despite optimum administration, an alternative triptan should be used. Triptans are usually given at the onset of headache, and not during aura.

Mini-prophylaxis for MAM

- First line: short course frovatriptan or NSAID.
- Second line: naratriptan or zolmitriptan.

Evidence base

Frovatriptan may be the most effective triptan in mini-prophylaxis for MAM. In an RCT the twice-daily (bd) dose (2.5 mg bd started 2 days before menstruation and continued for 6 days) was significantly more effective than the placebo at reducing headache frequency (incidence of migraine after 6 days of use, 41% vs. 67%, respectively). Naratriptan (1 mg bd for 5 days) and zolmitriptan (2.5 mg bd/three times daily for 7 days) have also been shown to be effective in MAM in RCTs.

Preventative treatment of episodic migraine

- This is recommended for patients who are adversely affected by migraine on ≥ 2 days per month.[9] Consideration should be given to the patient's comorbidities, other medications, and ease of compliance. Migraine prophylaxis is deemed successful when headache attacks decrease by at least 50% from the baseline rate in 3 months. A number of medications are for this indication. They are listed below. Selection between medications may vary depending on local guidelines, patient characteristics, and co-morbidities, as well as medication pricing. Currently in the UK, established oral therapies are used early in the treatment algorithm predominantly due to pricing, although this may change over the next few years. This is reflected in the suggested ordering of first, second-, and third-line agents, next.
- *First line*: beta-blockers (atenolol 50–200 mg, propranolol 40–240 mg, metoprolol 100–200 mg, bisoprolol 5–10 mg); topiramate 50–200 mg; ARBs (candesartan 8–32 mg, telmisartan 80 mg) (note risk of teratogenicity with topiramate).
- *Second line*: amitriptyline 10–100 mg, flunarizine 5–10 mg.
- *Third line*: acupuncture, onabotulinum toxin A, CGRP mAbs, CGRP receptor antagonists.

Evidence base

Angiotensin II receptor blockers (ARB): Small blinded cross-over studies have highlighted the potential efficacy of candesartan (40% responded to 16 mg/day).[10]

Anticonvulsants: Topiramate has been shown to be as effective as propranolol and valproate in reducing headache frequency. Two RCTs of topiramate showed a significant reduction in migraine frequency at doses of 100 and 200 mg/day.[11] A Cochrane systematic review concluded that sodium valproate was effective in reducing migraine frequency. Doses between 500 and 1500 mg/day reduced migraine frequency by >50% (OR 2.74, 95% CI 1.48–5.08).[12]

Despite guideline endorsement of gabapentin for migraine prevention, a systematic review found gabapentin to be ineffective.[12] Another study found no significant difference between gabapentin enacarbil and placebo. In a Cochrane systematic review, lamotrigine was found to be ineffective as migraine prophylaxis.

Antidepressants:

Tricyclic antidepressants: Amitriptyline, clomipramine, and doxepin were noted to be better than placebo in a network meta-analysis as preventative for episodic migraine. Amitriptyline had the greatest evidence with 5 trials included. Amitriptyline was most likely to produce a 50% reduction in episodic migraine headaches.[13]

β-blockers: Metoprolol and propranolol have been shown in several RCTs to be effective in migraine prophylaxis. In a meta-analysis, propranolol resulted in a 44% reduction in migraine frequency.[11]

Calcium channel blockers (CCB): Minimal effect over placebo was noted in trials of CCBs within a network meta-analysis. Tolerance may also develop and require a dose increase. The strongest evidence exists for verapamil (up to 480 mg/day in 3 divided doses) and flunarizine (5–10 mg/day).

CGRP Antagonists: Robust evidence exists for the efficacy of these agents in episodic migraine.[14] They include monoclonal antibodies and small-molecules, all of which have been shown to be effective for both acute treatment and prevention of episodic migraine.[15] Their wider use is limited currently by cost. Please refer to CGRP antagonists p. 380.

Other treatments and the placebo effect:

Riboflavin (vitamin B_2): A small RCT found that riboflavin 400 mg/day was associated with a >50% reduction in headaches (54% vs. 19%) and headache days (57% vs. 15%) compared to placebo.[16]

Magnesium: Limited quality evidence exists of the efficacy of magnesium in preventing migraine headaches. In 2 small RCTs 400–600 mg/day was used, which resulted in reduced headache days, headache severity, and use of analgesic agents.

NSAIDs: Naproxen, ibuprofen, ketoprofen, and fenoprofen have been shown to be more effective than placebo in migraine prevention in older RCTs.

Pizotifen: Several RCTs have shown the efficacy of pizotifen (1.5–3 mg/day in 3 divided doses) in migraine prevention.

Acupuncture: In a Cochrane systematic review of acupuncture in migraine prophylaxis (22 trials), acupuncture was found to be as effective as prophylactic drug treatment and produced fewer adverse effects. However, there appeared to be a significant placebo effect, as no significant difference was shown in efficacy between true and sham acupuncture.

Preventative treatment for chronic migraine

Chronic migraine is defined by the IHS as headache on at least 15 days per month, at least 8 of which have migrainous characteristics, for >3 months.

Treatment

- *First line*: amitriptyline 10–100 mg, atenolol 50–200 mg, candesartan 8–16 mg, telmisartan 80 mg, propranolol 40–240 mg, topiramate 50–200 mg (note the potential teratogenic potential of topiramate).
- *Second line*: flunarizine 5–10 mg.
- *Third line*: Onabotulinum toxin type A, anti-CGRP mAb monoclonal antibodies (fremanezumab, galcanezumab, eptinezumab, erenumab), CGRP receptor antagonists (atogepant and rimegepant), occipital nerve block.

Evidence base

There is less evidence for outcomes of pharmacological treatment of chronic migraine than for episodic migraine. In the UK, botulinum toxin A or an anti-CGRP antibody is recommended after failure of three pharmacological prophylactic treatments. It is unclear which of the two agents is superior at present. The PREEMPT clinical programme assessed botulinum toxin type A in chronic migraine in patients aged 18–65 years. The pooled analysis of both RCTs found that botulinum toxin type A was significantly more effective than placebo at reducing the number of headache days. However, it was not effective at reducing the amount of acute analgesia taken compared with placebo.[17]

RCTs have demonstrated moderate efficacy of CRGP mAbs for episodic and chronic migraine.[14] In one study, fremanezumab 225 mg monthly or 675 mg (first dose of subsequent quarterly schedule) decreased the mean number of migraine days per month by 1.5 and 1.3, respectively, at 3 months compared to placebo. A 50% reduction in mean number of monthly migraine days was achieved in 48% in the monthly dose group and 44% in the single higher dose group compared with 28% for the placebo group.[15]

Status migrainosus

Status migrainosus is defined as a severe migraine attack lasting longer than 72 h.

High-quality evidence for the treatment of status migrainosus is lacking. Treatment is based on patient factors and concomitant medication.

Treatment

- F*irst line*: IV fluids, magnesium sulphate 1–2 g IV, NSAID IV/PO and/or metoclopramide 10 mg IV, or sumatriptan 6 mg SC;
- *Second line*: dihydroergotamine 2 mg nasal spray (not within 24 h of triptan due to risk of hypertension and coronary vasoconstriction) or suppository, diclofenac 75 mg IM, chlorpromazine 25–50 mg IV or IM, prochlorperazine 12.5 mg IV or IM, or either prednisolone 50–100 mg PO or dexamethasone 4–16 mg IV.

Evidence base

IV aspirin and SC sumatriptan were both shown to be effective in acute migraine in a placebo-controlled RCT. Sumatriptan was more effective than aspirin but was associated with more adverse effects. Placebo-controlled trials have failed to show efficacy for corticosteroids in aborting migraine attacks or in reducing recurrence, but expert opinion suggests steroid use can be effective in severe migraine. Dihydroergotamine has been shown to be effective in open-label studies and is supported by expert opinion.[18]

Tension-type headache

TTH is the commonest headache type, with a lifetime prevalence of 42% in men and 49% in women. Although separated in the IHS classification, there are many similarities between migraine and TTH, and some experts consider them phenotypically distinct manifestations of the same disorder. TTH is typically bilateral and is described as a 'tightening' or 'pressure'. It can be associated with muscle tenderness around the head and neck and with nocturnal bruxism.[19]

Acute treatment of tension-type headache

- *First line*: NSAIDs and/or paracetamol.
- *Second line*: a combination of NSAIDs or paracetamol with caffeine.
- *Drugs to avoid*: opioids and triptans.
- *Also consider*: electromyography (EMG) biofeedback, cognitive behavioural therapy (CBT), and relaxation therapy.

Evidence base

Paracetamol 1 g has been found in most studies to be more effective than placebo at achieving freedom from pain at 2 h. Aspirin, diclofenac, and ibuprofen are also consistently more effective than placebo. Paracetamol and NSAIDs have similar efficacy, with no significant difference in adverse events. The efficacy of NSAIDs and paracetamol appears to be increased in combination with caffeine (64–200 mg). However, given the theoretical risk of caffeine withdrawal headache, this should be used as second-line therapy. Opioids increase the risk of MOH and should be avoided. The efficacy of triptans in TTH has not been consistently demonstrated. EMG biofeedback has been shown in a meta-analysis to have a moderate beneficial effect, and this effect was increased when used in combination with relaxation therapy. CBT has been shown to be more effective than placebo.

Treatment of chronic tension-type headache

- *First line*: acupuncture or amitriptyline.
- *Second line*: mirtazapine or venlafaxine.

Evidence base

Amitriptyline has been shown to be consistently effective as a prophylactic agent in several RCTs, with about 40% of patients showing significant improvement in headache severity in one trial. Mirtazapine at doses used for depression has been demonstrated to be effective in patients who have not responded to amitriptyline and may be useful in patients with TTH and co-morbid depression. An RCT of venlafaxine (150 mg/day) showed efficacy in reducing headache days in patients with episodic and chronic TTH. A Cochrane review concluded that acupuncture could be useful for TTH, showing benefit in headache and pain reduction persisting for up to 3 months after treatment. Trials investigating the use of occipital nerve block and botulinum toxin injection have not demonstrated effectiveness in the management of TTH.

Trigeminal autonomic cephalalgias (TACs)

TACs are a group of primary headache disorders that include cluster headache, PH, HC, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and cranial autonomic symptoms (SUNA). Although subtle differences exist between each disorder, a common pathophysiological mechanism is implicated, with abnormal activation of the trigeminal–parasympathetic reflex and centres controlling circadian rhythms, resulting in:

- unilateral trigeminal pain.
- rhythmicity.
- cranial autonomic dysfunction (e.g. lacrimation, rhinorrhoea).

Cluster headache

Cluster headache is characterized by severe unilateral attacks of orbital/supraorbital/temporal pain, associated with restlessness and cranial autonomic features (ptosis, miosis, conjunctival injection, lacrimation, nasal congestion, and rhinorrhoea). The attacks are short-lived (lasting from 15 min to 3 h), and patients may experience up to eight attacks a day. Commonly, the attacks occur at the same time every day, often waking the patient at night. In the episodic form, there are periods of remission, lasting months to years, while in the chronic form, there are not.

Acute treatment

- *First line*: high-flow oxygen (100% oxygen at 10–15 L/min for 10–20 min with a non-rebreathe mask) and/or nasal or SC triptan.
- *Second line*: intranasal lidocaine, SC octreotide, PO zolmitriptan.
- *Drugs to avoid*: ergots, hyperbaric oxygen, and opioids.

Evidence base

Oxygen has been shown in RCTs to be significantly more effective than placebo at reducing cluster headache severity. A double-blind, randomized, placebo-controlled cross-over trial of 109 patients with cluster headache found that treatment with high-flow oxygen (12 L/min) at the beginning of a cluster headache attack was more likely to result in the patient being pain-free at 15 min than with placebo (78% vs. 20%; $p < 0.001$).[20] Sumatriptan 6 mg SC was identified as being more effective than placebo at reducing headache at 15 min from moderate/severe to mild/no pain. It was effective in 75% of patients treated, and terminated attacks within 20 min. Intranasal lidocaine, SC octreotide, sumatriptan nasal spray, and oral and nasal forms of zolmitriptan are also more effective than placebo at reducing cluster headache intensity.[21]

Transitional therapy (mini-prophylaxis)

Preventative therapy should be started alongside abortive treatments in cluster headaches until a definitive preventative strategy is established.

- *First line*: corticosteroids or greater occipital nerve (GON) blockade.

Evidence base

- Corticosteroids have been shown to be effective as a bridging therapy for the initiation of preventative treatment. They are used for 2–3 weeks at doses of ≥30 mg/day prednisone or 4 mg bd

dexamethasone. There is a high risk of headache recurrence with dose tapering, therefore steroids should only be reduced and stopped once prophylactic agents are at therapeutic dosages.
- In severe intractable cluster headache, invasive measures, such as hypothalamic deep brain stimulation (DBS) and GON blockade, have shown promise in studies with adult patients.

Prophylactic treatment

- *First line*: verapamil.
- *Second line*: lithium, methysergide, topiramate, or galcanezumab.
- *Third line*: baclofen, gabapentin, intranasal capsaicin, melatonin, pizotifen, or valproate.

Evidence base

Verapamil is the first-choice agent for prophylaxis of episodic and chronic cluster headaches. It is more effective than a placebo at reducing cluster headache frequency. In one RCT 80% of those treated with verapamil responded with a reduction in cluster headache frequency, half within the first week. Verapamil and lithium appear to have similar efficacy in reducing attacks in RCTs, but verapamil is preferred as it has a faster onset of action and fewer drug interactions. Open-label studies suggest that methysergide and topiramate may be effective prophylactic agents, but they have not been assessed in RCTs.

Paroxysmal hemicrania and hemicrania continua

PH and HC are indomethacin-responsive unilateral headache disorders associated with autonomic features. PH is distinct from cluster headache in that attacks are usually shorter in duration, lasting between 2 min and 30 min, and more frequent, occurring >5 times per day. It is classically highly responsive to indomethacin. HC is continuous in nature, with the majority of patients suffering from unremitting pain.

Treatment

- *First line*: indomethacin.
- *Second line*: other NSAIDs or verapamil.
- *Third line*: ergots or topiramate.

Evidence base

Indomethacin is so effective in terminating PH and HC attacks that a response to indomethacin (recommended starting dose 75 mg/day) is part of the diagnostic criteria.[22] Verapamil and some other NSAIDs (piroxicam, aspirin, cyclo-oxygenase 2 (COX-2) inhibitors) also have some efficacy in PH in open-label studies.

Other headache syndromes

In addition to PH and HC, other headache types which may respond well to indomethacin include Valsalva-induced headache, primary cough headache, primary exertional headache, primary headache associated with sexual activity, and primary stabbing headache. The recommended starting dose of indomethacin is 75 mg (increased to 150 mg daily, according to response).

Hypnic headache generally responds to caffeine and may respond to indomethacin, lithium, flunarizine, and melatonin as described in case reports.

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)

SUNCT is characterized by very short, severe, unilateral attacks of headache, centred around the ophthalmic trigeminal area, associated with conjunctival injection and watering. It is a rare disorder and is typically seen in middle and older age (40–70 years). Triggers for an attack include any action, which stimulates an area within the trigeminal-innervated zone, e.g. brushing hair, eating, or talking. The disorder is so rare that there are no published placebo-controlled trials of treatment.

SUNA is distinguished from SUNCT by the presence of either conjunctival injection or lacrimation but not both.[23]

Preventative treatment

- *First line*: lamotrigine up to 700 mg/day.
- *Second line*: oxcarbamazepine (up to 2400 mg bd), duloxetine, (up to 120 mg/day), carbamazepine (up to 1600 mg/day), topiramate (up to 800 mg/day) gabapentin (up to 4800 mg/day), pregabalin (up to 600 mg/day), lacosamide (up to 400 mg/day) and mexiletine (up to 1200 mg/day).
- *Refractory cases*: Hypothalamic DBS, occipital nerve stimulation, and microvascular decompression of the trigeminal nerve may have a role.

Evidence base

In a prospective open-label study with meta-analysis,[24] lamotrigine was shown to be effective (in 56% of 161 patients) as a prophylactic agent in SUNCT/SUNA. Intravenous lidocaine given for 7–10 days led to improvement in 90% of patients. The same study demonstrated efficacy of oxcarbamazepine (46%), duloxetine (30%), carbamazepine (26%), topiramate (25%), pregabalin and gabapentin (10%).

Secondary headache

In this chapter, only IIH and MOH will be discussed.

Idiopathic intracranial hypertension

IIH typically occurs in women who are overweight and of childbearing potential. It is also associated with excessive vitamin A intake, growth hormone therapy, and tetracycline antibiotics, and has been linked with certain systemic illnesses, including systemic lupus erythematosus (SLE), hypoparathyroidism, sleep apnoea, and polycystic ovary syndrome (PCOS). Patients usually present with a diffuse headache, worse in the morning and on lying down and exacerbated by the Valsalva manoeuvre. They may also experience nausea, vomiting, and visual disturbances, including diplopia and obscurations, and can have papilloedema. Treatment is aimed at lowering intracranial pressure (ICP) and reducing the risk of permanent optic nerve damage. If vision is imminently threatened, therapeutic lumbar puncture is required, often followed by cerebrospinal fluid (CSF) diversion procedures such as lumboperitoneal shunting or optic nerve sheath fenestration.

Medical management

- *First line*: acetazolamide.
- *Second line*: corticosteroids, loop diuretics, topiramate.
- *Other management strategies*: repeated lumbar puncture (LP).

Evidence base

The IIH Treatment Trial[25] found that acetazolamide significantly improved visual function, papilloedema grade, and reduced body weight when compared with placebo at six months with mean doses of 2.5 g/day. However,19% withdrew from the trial due to adverse effects, all except one of whom received acetazolamide. The addition of furosemide has been shown to be effective in reducing pressure and papilloedema in case series. Topiramate has some carbonic anhydrase activity and is associated with weight loss, which makes it an attractive alternative. It was shown to have similar efficacy to acetazolamide in one comparative study, but more robust evidence is lacking. Due to the associated weight gain, corticosteroids are not recommended for long-term management of IIH but can be used as bridging therapy prior to surgery.

Medication overuse headache

MOH occurs in patients with primary headache disorders who take acute analgesic medication regularly for >3 months. The culprit agents are:

- ergots, opioids, and triptans for ≥10 days per month.
- aspirin, NSAIDs, and paracetamol, alone or in combination for ≥15 days per month.

Management

The implicated analgesic should be withdrawn. Simple analgesics can be abruptly stopped, while opioids, benzodiazepines, and barbiturates will require gradual dose reduction with close monitoring. The majority of patients can be managed in the community, but a proportion may benefit from admission and IV hydration.

If drug treatment is also required:

- *First line*: topiramate 100–200 mg/day.
- *Second line*: amitriptyline (up to 50 mg/day), corticosteroids (up to 60 mg/day), or NSAIDs.

Evidence base

Topiramate was found to be effective in reducing headache frequency in MOH in three RCTs. Corticosteroids have shown conflicting results. One RCT showed no efficacy with 60 mg prednisolone, while another found that treatment with 100 mg prednisolone significantly shortened headache duration, compared to placebo. Amitriptyline may be effective in MOH but has not been assessed in placebo-controlled trials. NSAIDs have been used for MOH but are not first-line, as they can also cause MOH. Naproxen has been shown in one uncontrolled study to be effective in reducing the intake of analgesics and headache severity when combined with amitriptyline.[26]

CGRP mAbs are equally effective at reducing migraine in those with or without MOH, and real-world evidence suggests that CGRP mAbs can be very effective in individuals with MOH.[14]

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Chapter 2

Vertigo

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Introduction

Dizziness is one of the most common neurological complaints, with 15–35% of adults reporting the symptom at some point in their lives. It is associated with anxiety, handicap, and avoidance behaviour, resulting in significant functional impairment. Dizziness presents a challenge for the physician, as both establishing a diagnosis[1,2] and achieving adequate symptom control can be difficult. The word dizziness is used by patients to describe a variety of symptoms, from light-headedness to imbalance to true vertigo. Therefore, one first needs to establish what the patient means by the term 'dizziness'. Patients may find this difficult, and use of analogies such as 'spinning like a merry-go-round', 'rocking as if on a boat', off-balance, lightheaded, or faint, may help the patient to more accurately describe their symptoms.

Vertigo, when strictly defined as an illusion of either oneself or the environment moving, is a reliable symptom. It indicates the involvement of the semicircular canals or otolith organs and/or their central projections. Localizing the exact site of the lesion relies upon the presence of associated symptoms and clinical signs. One approach is to begin by distinguishing peripheral from central vertigo. Another is to consider the commoner diagnoses first.

Peripheral vertigo is typically positional, associated with constitutional upset, nausea, and vomiting, and either occurs in isolation or in association with hearing loss and/or tinnitus. Central vertigo is rarely an isolated symptom and is often accompanied by dysarthria, paraesthesiae, weakness, diplopia, incoordination, or other brainstem or cerebellar symptoms.

The commonest causes of dizziness in general practice are benign paroxysmal positional vertigo (BPPV), postural hypotension, vestibular neuronitis/labyrinthitis, and vestibular migraine. Rarer causes include posterior circulation (brainstem or cerebellar) stroke, multiple sclerosis (MS), and Ménière's disease.

This chapter covers the evidence-based treatment options for the commoner peripheral and central vestibular disorders. It should be noted that recent evidence supports the clinical finding that traditional 'vestibular sedatives', e.g. antidopaminergics and antihistamines, have no effect on vestibulo-ocular function or the perception of self-motion and their effect is primarily antiemetic.

Classification

The International Classification of Vestibular Disorders defines vertigo as 'the sensation of self-motion when no motion is present or altered sensation of motion when motion occurs'. Sub-classification of vertigo is difficult, and no strict universally acknowledged system exists. Vertigo is often defined on the basis of the character of the vertigo or the underlying aetiology.

Classification by vertigo character

Vertigo can be spontaneous or triggered. Spontaneous vertigo occurs without any internal or external perturbation. The main types of triggered vertigo are tabulated in Table 2.1.

Table 2.1 Examples of triggered vertigo

Trigger	*Definition*
Positional	Occurs after a change in head position
Head motion	Occurs during head movement
Visually induced	Induced by busy visual environments or full-field motion (such as a train coming into the station while standing on the platform, or walking along a supermarket aisle)
Sound induced	Auditory stimuli induce vertigo (Tullio phenomenon)
Valsalva induced	Any bodily manoeuvre that increases intracranial or middle ear pressure
Orthostatic	Due to a change in body posture from sitting or lying to standing
Other	For example, dehydration, medication, environmental pressure changes, exercise, hormones, and hyperventilation

Classification by vertigo aetiology

The causes of vertigo can be divided into peripheral and central types, as described in Table 2.2.

Table 2.2 Common peripheral and central causes of vertigo

Peripheral	Central
Acoustic neuroma	Posterior circulation stroke
BPPV	Episodic ataxias
Ménière’s disease	Vestibular migraine
Vestibular neuronitis/labyrinthitis	Multiple sclerosis
Vestibular paroxysmia	

Peripheral causes of vertigo

Benign paroxysmal positional vertigo

While BPPV is the commonest cause of peripheral vertigo, accounting for 20% of all cases, it remains under-diagnosed, particularly among the elderly population whose description of 'dizziness' may be vague, and manifest primarily as a sense of imbalance or dysequilibrium.

BPPV is caused by calcium carbonate crystals (otoconia or canaliths) settling within the endolymphatic fluid of one or more semicircular canals, commonly the posterior semicircular canal. Horizontal canal BPPV is much less common, responsible for only 10–20% of cases, and anterior canal BPPV accounts for 5%. Although it is usually idiopathic, BPPV may be caused by head trauma (when it is often bilateral) or following vestibular neuronitis.

Patients with BPPV present with violent attacks of vertigo (typically seeing the room spin), triggered by a specific and reproducible change in head position. These last only seconds, but patients may report longer duration, such is its severity, and the inaccuracy of subjective recall of time. Attacks abate if the head is kept completely still, but a change of position, often in an attempt to stop the vertigo, can provoke a further attack. Nausea is common, but vomiting is rare, given the brevity of each attack.

A history of recurrent vertigo episodes triggered by movement suggests BPPV, and the diagnosis can be confirmed with the Dix–Hallpike manoeuvre.

Treatment

- *First line*: Repositioning manoeuvres (Epley or Semont) for typical posterior canal BPPV.
- *Supportive*: There are conflicting data on the effectiveness of vestibular sedative medications for the treatment of BPPV and other causes of peripheral vertigo. Betahistine 24 mg/day may assist in conjunction with repositioning manoeuvres.

Evidence base

Multiple systematic reviews and meta-analyses have confirmed the safety and efficacy of repositioning manoeuvres, such as the Epley and Semont manoeuvres, for treating posterior canal BPPV.[3] One meta-analysis of nine RCTs, comparing repositioning manoeuvres to sham procedures, found that the treatment arms were more likely to demonstrate symptom resolution (OR 4.6, 95% CI 2.8–7.6) and a negative Dix–Hallpike test (OR 5.2, 95% CI 3.0–8.8) at the time of the first follow-up.[1] A separate meta-analysis of 505 patients, with a mean follow-up of 16 days, found an absolute risk reduction of 41% in those exposed to treatment compared with no treatment (NNT = 2).[4]

There are very few RCTs assessing the efficacy of medication for the symptoms of BPPV. One study randomizing 156 patients to either the Semont manoeuvre, flunarizine (10 mg/day) or no treatment reported symptom resolution of 57.7% with flunarizine, 94.2% with the Semont manoeuvre, and 34.6% with no treatment. A further double-blind, placebo-controlled RCT in 72 patients with posterior canal BPPV suggested that combining betahistine 24 mg twice daily for 1 week with the Epley manoeuvre improved quality of life above the Epley manoeuvre alone. The underlying mechanism of this response is unclear, given that BPPV is a 'mechanical' problem, but may be explained by improving compliance with corrective manoeuvres through the sedative effects of betahistine and/or by increasing inner-ear blood flow and vasodilation thereby relieving inner pressure. A systematic review of 5 RCTs concluded that betahistine 24–48 mg/day was effective and safe in the treatment of peripheral vertigo. A recent blinded-assessment RCT conducted in Korea (n = 1050, 518 intervention arm) found vitamin D 400 IU and calcium carbonate 500 mg twice a day for 1 year when serum vitamin D level was <20 ng/mL resulted in fewer attacks of BPPV in the intervention group than in the observation group (37.8 vs. 46.7%, $p = 0.005$). A subsequent meta-analysis by the same group containing 5 trials (4 non-randomized) supported the supplementation of vitamin D, finding a significant preventive effect on recurrences of BPPV (RR = 0.37; 95% CI = 0.18–0.76; $p = 0.007$). Benzodiazepines have not shown any difference when compared to placebo for BPPV.

Vestibular neuronitis

Vestibular neuronitis, or neuritis, is an inflammatory disorder of the vestibular portion of the eighth cranial nerve of presumed viral aetiology. Estimated incidence is 3.5 per 100 000 population, although it may be overdiagnosed and misdiagnosed. For many non-specialists, the term 'vertigo' has become synonymous with 'labyrinthitis', a label that is often attached to peripheral dizziness, presumed to be benign in origin. True labyrinthitis, however, refers to inflammation of the whole labyrinth (vestibular *and* cochlear parts) and is exceptionally rare in clinical practice.

Clinical features

Features of vestibular neuronitis include rapid onset of severe, persistent vertigo (hours to days). Nausea, vomiting, and imbalance are seen in virtually all cases. The clinical examination reveals spontaneous unidirectional horizontal and torsional nystagmus (with the fast phase always beating away from the affected side, irrespectively of whether the patient is looking right or left). Patients with vestibular neuritis have unilateral loss of the vestibulo-ocular reflex (VOR). The head impulse test, a direct test of the VOR, will therefore be abnormal when a small-amplitude, but fast, head rotation is performed towards the affected side.

Treatment

1. Acutely for severe symptoms

First line:

- IM or buccal prochlorperazine 5–10 mg IV/IM every 3–4 hours as needed
- Dimenhydrinate 50 mg IV every 4 to 6 hours prn

Second line:

- Diazepam 2 mg IV or 5 mg IM/PO every 6 hours as needed

2. Subsequently or for moderate symptoms

- Oral or buccal antidopaminergic (e.g. prochlorperazine 3–6 mg BID) or
- Antihistaminergic agents (e.g. dimenhydrinate 50–100 mg orally every 4–6 hours (max: 400 mg/day), meclizine 25 mg orally every 6 hours as needed (sedating)) or
- Anticholinergic (e.g. hyoscine 0.3 to 0.6 mg daily for a maximum of 3 days).

Patients should be encouraged to resume physical activity as soon as possible and be given vestibular exercises.

Evidence base

An RCT found that dimenhydrinate 50 mg was superior to lorazepam 2 mg for the relief of vertigo in patients with vestibular neuritis presenting to the emergency department.[5] In a small prospective study of 39 patients, vestibular exercises were shown to improve central vestibulo-spinal compensation after the acute symptoms had resolved.

Corticosteroids, antivirals, and benzodiazepines are not routinely used, as there is conflicting evidence that they improve long-term outcomes.[6]

Ménière's disease

Ménière's disease is a rare condition. Incidence estimates vary between 7.5 and 160 per 100 000, depending on the country and the diagnostic criteria used. It is caused by excess endolymphatic fluid pressure. 'Endolymphatic hydrops' is the pathological hallmark of this condition. The diagnosis is made on the basis of clinical findings. The American Academy of Otolaryngology Head and Neck Surgery guidelines state that a diagnosis of 'definite' Ménière's disease requires two or more spontaneous episodes of vertigo, each lasting 20 min or longer, audiogram-confirmed hearing loss, tinnitus or aural fullness in the affected ear, and exclusion of other causes (typically with gadolinium-enhanced MRI of the brain).

Clinical features

Patients often present with spontaneous, episodic, disabling vertigo (lasting minutes to hours), in association with unilateral tinnitus, aural fullness, and unilateral fluctuating deafness. Typically, there is nausea and vomiting, with imbalance that may last for several days. Examination reveals horizontal torsional nystagmus in the acute phase, together with an impaired ipsilateral VOR. Some patients develop otolithic crises, termed Tumarkin attacks, leading to severe lateropulsion and falls. All the symptoms may not be present simultaneously, particularly in the early phases of the disease. The course is usually relapsing–remitting, although some patients may have a more progressive course. Episodes can occur as often as every few days, although more typically every few months. Spontaneous remission is recognized, although symptoms may recur later in life. Audiometric testing may reveal a low-frequency sensorineural deafness, which may fluctuate over time, and bithermal caloric testing rotational tests with electro-nystagmography may reveal a reduced unilateral vestibular response. Vestibular-evoked myogenic potentials and electro-cochleography can assist with the diagnosis but are not routinely used outside highly specialized centres.[7]

Treatment

There is no cure for Ménière's disease; the aim of treatment is to reduce symptom severity.

- *Acute*: control of vertigo and nausea with antiemetics, antihistamines, and other centrally acting sedative medication.
- *Long-term treatment*:
  - *First line*: salt restriction and diuretics (e.g. bendroflumethiazide);
  - *Second line*: betahistine 24 mg bd–48 mg tds;
  - *Third line*: steroids administered via intratympanic injection (often patients prefer oral steroid course unless contraindicated).
  - *Fourth line*: medical (gentamicin) or surgical labyrinthectomy.

If attacks continue despite salt restriction and diuretics, an increasing dose of betahistine can be tried, although, in severe attacks or where attacks are frequent, intratympanic steroids or gentamicin are preferred.

Evidence base

Salt restriction (2–3 g) and diuretics have traditionally been considered the best medical therapy for Ménière's disease, reportedly controlling vertigo in 58% of patients and stabilizing hearing in 69%.[8] The effect of diuretics has not, however, been systematically replicated.

Betahistine has been used in the treatment of vertigo for over 50 years.[9] A 2001 Cochrane systematic review concluded that none of six trials assessed the effect of betahistine adequately, although most reported a reduction of vertigo.[4] One observational study ($n = 112$) suggested high-dose betahistine (48 mg tds) was significantly superior to 24 mg tds, particularly at 12 months.[10] Doses as high as 480 mg/day have been used successfully in individual patients. An RCT comparing placebo ($n = 74$), low-dose betahistine (2 × 24 mg daily ($n = 73$)), or high-dose betahistine (3 × 48 mg daily ($n = 74$)) over nine months, found no significant difference in the incidence of attacks between the groups.[11]

Intratympanic corticosteroid and gentamicin injections: there is limited evidence from small trials for the use of intratympanic membrane injections of corticosteroids and gentamicin in the treatment of Ménière's disease.

A Cochrane systematic review of corticosteroids in 2011 found only one placebo-controlled trial for intratympanic steroids ($n = 22$). The study showed that, after administration of 4 mg/mL of intratympanic dexamethasone for 5 consecutive days, there were statistically significant improvements in vertigo, as evidenced by improved functional level (90% vs. 42%), change in the Dizziness Handicap Inventory score (60.4% vs. 41.3%), and mean vertigo subjective improvement (90% vs. 57%), compared to placebo. These changes were maintained over a follow-up of 24 months.[12]

A 2011 Cochrane systematic review investigating the use of intratympanic gentamicin identified two placebo-controlled trials ($n = 50$), which showed a significant reduction in vertigo with treatment. However, it was recommended that this treatment be reserved for patients with pre-existing hearing loss, as 20% will develop a degree of deafness as a complication. Likewise, administration to only one ear is recommended, despite around

40% of patients developing bilateral disease after 20 years.[6] One cohort study, comparing intratympanic methylprednisolone with gentamicin, found that 82.9% of the gentamicin group and 48.1% of the steroid group achieved complete control of vertigo ($p = 0.004$), with better control of tinnitus and aural fullness with gentamicin than methylprednisolone ($p \leq 0.002$). A second study, a prospective RCT, showed similar results in that the frequency of vertigo attacks in refractory Ménière's disease was preferentially reduced with gentamicin (93% vs. 61%).[13] More recently, a prospective RCT comparing the two drugs found no significant differences between intratympanic methylprednisolone and gentamicin in reducing vertigo frequency over the final 6 months of treatment, compared to the 6 months prior to treatment. This trial indicated that methylprednisolone injections are a non-ablative, effective treatment for refractory Ménière's disease, but the choice between methylprednisolone and gentamicin should be made based on clinical knowledge and patient circumstances.[14]

Vestibular paroxysmia

This is a rare, but important, syndrome characterized by brief (milliseconds to seconds) attacks of vestibular and auditory deficits, including vertigo, imbalance, and tinnitus. It is thought to arise from neurovascular cross-compression of the vestibular nerve and an offending vessel. It is important to consider the diagnosis in patients presenting with paroxysmal spontaneous vertigo, as it is readily treatable.

Treatment

- *First line*: carbamazepine or oxcarbazepine.
- *Second line*: gabapentin, lamotrigine, phenytoin, or sodium valproate.
- *Refractory symptoms*: microvascular neurosurgical decompression of the eighth cranial nerve.

Evidence base

Where there are >2 severe episodes per month, treatment with carbamazepine 200–600 mg/day may be successful. Both symptoms of tinnitus and vertigo should respond to carbamazepine, and such a response is often considered part of the proposed diagnostic criteria for the condition. Antiepileptic drugs (AEDs), such as gabapentin, lamotrigine, phenytoin, and sodium valproate, are alternatives for patients who do not tolerate carbamazepine, although the evidence for these is based on case studies and expert consensus, as no RCTs have been conducted.[15]

Central causes of vertigo

Vestibular migraine

A diagnosis of vestibular migraine is not widely recognized outside specialist practice, but approximately half of patients with classical migraine will report dizziness and vertigo, and 20% fulfil the criteria for migrainous vertigo. Patients with vestibular migraine commonly report spontaneous or positional vertigo lasting hours to days. The typical patient is a migraineur who has noticed a recent increase in headache frequency and, over the same period, developed vestibular episodes, with headache and vertigo not necessarily occurring together. Other migrainous features, such as photophobia, phonophobia, and nausea, are often present during the vertiginous episode, as well as increased motion sensitivity, i.e. an aversion to self-movement and external motion.

Vestibular migraine remains a diagnosis of exclusion, although diagnostic criteria have now been proposed and are included as an appendix in the latest International Classification of Headache Disorders (3rd edition). Clinical examination during an attack may reveal a number of different oculomotor abnormalities (in up to 60% of cases), including nystagmus of a central type. Thus, acute brain imaging may be required on the first presentation. The diagnosis is aided by a previous history of similar symptoms, or a strong personal or family history of migraine. It should be noted that BPPV, Ménière's disease, anxiety disorders, and orthostatic hypotension are more common in migraine sufferers than in controls and may cause diagnostic confusion.

Treatment

- The therapeutic recommendations for vestibular migraine are currently based on the guidelines for migraine treatment, including administration of β-blockers or amitriptyline for a period of 3–6 months. Alternatives are topiramate or valproic acid, although these have only been described in small observational studies of vestibular migraine (see Prophylaxis of episodic migraine p. 7).

Evidence base

A single RCT has compared venlafaxine, valproate, and flunarizine and found that a decrease in Dizziness Handicap Inventory total score was shown following treatment with all three medications, with no obvious differences between the groups.[16] A further RCT compared flunarizine combined with betahistine to betahistine alone, revealing an improvement in the frequency of vertigo in the flunarizine group, but no difference in duration and severity of symptoms.

A recent systematic review and meta-analysis included 13 studies and reported improvements in Dizziness Handicap Inventory and frequency of vertigo with anti-seizure medicines, calcium channel blockers TCAs, ß-blockers, SNRIs, and vestibular rehabilitation. However, due to the heterogeneity and variable reporting outcomes they concluded that strong recommendations could not be made for a preferred treatment modality.[17]

Posterior circulation stroke

Posterior circulation stroke causes abrupt onset of vertigo (within seconds), often accompanied by occipital headache. Other associated signs may include gait or limb ataxia, facial numbness, Horner's syndrome, hearing loss, contralateral hemiparesis, and hemisensory loss, reflecting simultaneous involvement of other cerebellar or brainstem structures. Importantly, the head impulse test remains normal in posterior circulation stroke, with the exception of rare, isolated strokes mimicking a peripheral vestibulopathy. Immediate brain imaging is indicated in suspected strokes of the posterior circulation, as these patients may require thrombolysis or even surgical intervention. Red flags in cases of acute dizziness include unilateral hearing loss, other neurological symptoms or signs, new headache, and a normal VOR as assessed by the head impulse test.

Treatment

- As per stroke (see Chapter 4, Cerebrovascular disease).

Multiple sclerosis

The vestibular system is frequently involved in MS. In fact, vertigo is much commoner than hearing impairment in this group of patients. Vertigo is seen as an initial presentation in 5% of patients with MS and will ultimately occur in 40% of patients with established MS. Patients usually describe vertigo that is torsional (rotational) but can be in any direction and can be positional. Physical examination during an acute attack of vertigo often reveals spontaneous or positional nystagmus which may be of a 'central' type—persistent and without latency (in contrast to BPPV, which has a 3–4 s latency and is short-lived). There may also be gait and limb ataxia, dysarthria, and slow pursuit movements related to cerebellar dysfunction.

It is important to remember that BPPV remains the commonest cause of vertigo and imbalance, irrespective of any coexisting neurological syndrome. Thus, vertigo should not be automatically attributed to demyelination in a patient with MS.

Treatment

As per MS (see Chapter 7, Other inflammatory disorders of the central nervous system).

- In the acute setting, management will be dependent upon the cause of the vertigo. In a 4-year retrospective study of vertigo in MS patients, BPPV was found to cause the majority of cases and resolved with repositioning manoeuvres.

Episodic ataxias

The episodic ataxias are a group of seven (EA1 through to EA7) dominantly inherited channelopathies, of which type 1 and type 2 are the commonest, and result from mutations in a voltage-gated potassium channel and a brain-specific subunit of the P/Q type calcium channel, respectively. The syndrome is characterized by stress-induced attacks of ataxia and dysarthria, with interictal nystagmus and in 30–50% late-onset progressive ataxia.

Treatment

EA1: acetazolamide (250–1000 mg/day), carbamazepine (up to 1600 mg/day), or sodium valproate.

EA2: first line: acetazolamide (start at 125 mg od, may require up to 8–30 mg/kg/day in one to four divided doses, not to exceed 1 g/day);

second line: aminopyridines (4-AP (5–10 mg tds) or 3,4-DAP (5 mg/day–20 mg tds)); flunarizine (5–10 mg/day)

Evidence base

Patients with EA1 have a variable response to acetazolamide[18]; hence, carbamazepine or sodium valproate are often used on the basis of observational studies and expert consensus. There have been no controlled studies comparing the efficacy of different drugs.

A small RCT of EA2 patients showed a significant reduction in the number and duration of attacks with 4-aminopyridine compared to placebo. There is some evidence from small trials that 4-AP may be more effective than equivalent doses of 3,4-diaminopyridine (3,4-DAP) for the control of symptomatic downbeat nystagmus (DBN) (often observed in EA2).[19,20]

Newer treatments for oscillopsia

Oscillopsia refers to the illusion of oscillation of the visual world and, in the clinical setting, denotes the presence of nystagmus. Patients with oscillopsia may describe blurring, 'wobbly', or 'jumpy' vision.[21] Further in-depth information with regard to subtypes and aetiology is beyond the scope of this book. For a review of the causes and therapy of oscillopsia, the reader is referred to the 2011 EFNS Task Force guidance.[22] Off-licence pharmacological treatments of oscillopsia used by some specialists include the following, although no double-blind clinical trials are available:

1. Aminopyridines, e.g. 3,4-DAP (20 mg tds) and 4-AP (10 mg tds), may be used for DBN.[23–25]
2. Modified amino acid acetyl-DL-leucine (5 g/day) may be used for cerebellar ataxia.
3. Gabapentin, valproate, clonazepam, memantine, and biperiden can be tried for continuous (rather than positional or paroxysmal) oscillopsia. There is variable response to these drugs, so each should be tried individually before being combined.
4. In one case series, treatment with baclofen (5–10 mg tds) resulted in an improvement in several patients with upbeat nystagmus.

Evidence base

For downbeat nystagmus, a condition commonly due to cerebellar degeneration or ischaemia, one RCT showed that 57% of patients responded to treatment, as measured by tandem-walk, 'get-up-and go' tests, and measurements of visual acuity. A recent case series of 13 patients showed that the modified amino acid acetyl-DL-leucine (5 g/day) exerted a significant effect on cerebellar ataxia after only 1 week.[26]

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Chapter 3

Epilepsy

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Introduction

Epilepsy is one of the most common neurological conditions world-wide with a lifetime prevalence of approximately 1%. Importantly, about two-thirds of patients with epilepsy should expect to secure seizure control with appropriately chosen antiseizure medications (ASMs).

Epilepsy is not a single condition but a diverse group of disorders, comprising different seizure types and over 30 electro-clinical syndromes.

There is an ever-growing number of ASMs to treat epileptic disorders, each with its own indications and distinct side effect profiles.

This chapter will address the treatment of epilepsy in adulthood, focusing first on general principles of epilepsy management followed by specific scenarios including women of childbearing potential, status epilepticus, and rare epilepsy syndromes such as Lennox–Gastaut and Dravet syndrome for which there are newly licensed therapies.

Classification

Seizures can be divided into focal (partial) and generalized types. Generalized seizures are further subcategorized, predominantly based on their motor features (see Fig. 3.1). These subtypes guide ASM selection. Certain ASMs are preferentially used for the management of specific seizure types, e.g. ethosuximide for the treatment of absence seizures, or avoided in other seizure types, e.g. carbamazepine, which may exacerbate myoclonic seizures. Focal seizures can be subdivided based on their semiology, site of onset, pattern of spread, involvement of arousal centres and the presence or absence of evolution to bilateral convulsive activity (secondary generalization).

The International League Against Epilepsy (ILAE) defines epilepsy as: ‘a disease of the brain defined by any of the following conditions: 1) A minimum of two unprovoked seizures occurring >24 h apart; 2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk after 2 unprovoked seizures, occurring over the next 10 years; 3) Diagnosis of an epilepsy syndrome’.[1]

A significant proportion of patients with epilepsy can be classified as having a distinct epilepsy syndrome and specific aetiology (see Fig. 3.2). The

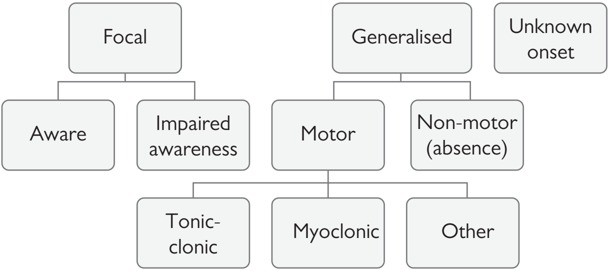

Fig. 3.1 ILAE seizure classification. Based on Fisher *et al*., 2017.[1]

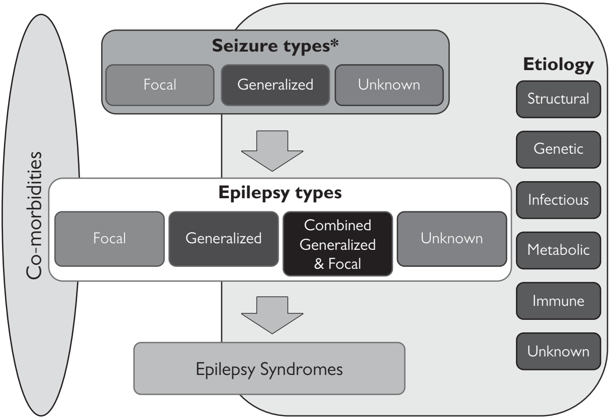
Seizure types*
Focal
Generalized
Unknown
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown
Co-morbidities
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes

Fig. 3.2 ILAE framework for classification of the epilepsies. Reproduced with permission John Wiley and Sons. Scheffer IE *et al.*, 2017.[2]

electro-clinical syndromes typically comprise distinct clinical and epidemiological features, combined with associated electroencephalogram (EEG) or radiological findings. Aetiology can vary widely and may include structural, metabolic, immunological, infectious, or specific genetic diagnoses. Both the electro-clinical syndrome and underlying aetiology help predict prognosis and guide treatment strategies:

1. The underlying aetiology may require the use of disease-specific therapies in conjunction with ASMs. For instance, immunosuppressive therapy for autoimmune encephalitis, the ketogenic diet for GLUT-1 deficiency or surgery for structural lesions.
2. Several recently available medications are only licensed for specific conditions, e.g. cannabidiol for Lennox–Gastaut syndrome and Dravet syndrome.

When to initiate treatment

Several studies have demonstrated that a large proportion of patients treated for epilepsy have an alternative diagnosis. The proportion of epilepsy misdiagnosis varies depending on the study population. Two UK studies found misdiagnosis rates of 16–23% in general practice,[3,4] and 26% in epilepsy clinics.[5] Non-epileptic attack disorders (NEADs)/psychogenic non-epileptic seizures (PNES) provide the most diagnostic difficulty. Alternative diagnoses should be considered both prior to initiation of therapy and later if seizure control proves unexpectedly difficult or variable.

Patients with a ‘first fit’ need a medical review, blood biochemistry, and an electrocardiogram (ECG). Most adults will require imaging, preferably a brain MRI as well as an electroencephalogram (EEG).

Factors influencing when to start treatment

Following an unprovoked first seizure, the chance of a second unprovoked seizure within the next 2 years is >40%. Factors that increase the risk for subsequent development of epilepsy include:

- ≥2 seizures.
- underlying neurological disorder/deficit.
- abnormal EEG.
- significant brain imaging abnormalities.
- nocturnal seizure.

High-risk individuals with one or more of the above factors may be started on an ASM after a single seizure, after careful discussion with the patient.

Individuals who are at low/medium risk of seizure recurrence typically start treatment after the second seizure. The following factors influence when to initiate treatment and which specific ASM to consider:

- seizure symptomatology and duration.
- psychosocial morbidity, including driving regulations.
- medical comorbidity.
- pregnancy and family planning.

Treatment strategies

Monotherapy

ASM monotherapy should be used where possible. ASMs are titrated to a level sufficient to control seizures or to the maximum tolerable level. If treatment is unsuccessful, then monotherapy with an alternative first- or second-line agent is recommended. The new drug should be started, and the first drug slowly tapered when the new drug is at appropriate maintenance levels. Two to three different agents should ideally be trialled as monotherapy, before combination therapy is considered (although practice varies with many opting to initiate combination therapy after a single failed agent, especially if seizure frequency improves to a significant degree with the first agent). Fifty per cent of patients should expect to be seizure-free on their first ASM. A third of the remainder should be rendered seizure-free with a different ASM or combination therapy, and of those still having seizures, a further quarter will become seizure-free after a third agent. Overall, a total of~70% of patients can be expected to be seizure-free after a trial of up to three ASMs.[6]

Combination therapy

If monotherapy fails, it may be necessary to add an adjunct. The ASM which has proved most effective should be used with an alternative first- or second-line drug. Care needs to be taken with polytherapy, to ensure that potential pharmacokinetic interactions and pharmacodynamic side effects are discussed with the patient and adjusted for.

Drug-resistant epilepsy

In adults, drug-resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

10–20% of people with epilepsy will not be controlled sufficiently by ASMs. In these cases, the most effective regime should be continued, and epilepsy surgery should be considered. Surgery may be resective or non-resective, depending on whether epileptogenic foci are present. Non-resective surgical options include vagus nerve stimulation, thalamic deep brain stimulation (DBS), subpial transections, and corpus callosotomy.

Pharmacological treatment

(adapted from AAN[7]/NICE[8]/SIGN guidelines[9])

The appropriate selection of an ASM depends on several factors including age, gender, co-prescribed medications, comorbidities, as well as the patient's epilepsy syndrome and predominant seizure types.

In all the guidelines listed sodium valproate is considered a first-line agent for several seizure types. In the UK this contradicts more recent statements from the MHRA commission on human medicines (CHM). The CHM recommends that, considering its teratogenicity and its potential effects on male fertility, no patients <55 years old (male or female) should be commenced on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment.[10] Therefore, although valproate has been included in the following treatment recommendations, its use in the UK is reserved for refractory cases rather than early therapy.

Focal-onset (partial) seizures

Focal epilepsies have varied clinical manifestations, including motor, sensory, autonomic, and dyscognitive phenomena, and may lead to bilateral (generalized) convulsive seizures.

Treatment

- *First-line*: carbamazepine or lamotrigine.
- *Second line*: levetiracetam, oxcarbazepine.
- *Third line*: acetazolamide, brivaracetam, cenobamate, clobazam, eslicarbazepine acetate, gabapentin, lacosamide, perampanel, phenobarbital, phenytoin, pregabalin, tiagabine, topiramate, valproate (see above discussion on valproate use in <55-year-olds) or zonisamide.

Evidence base

There have been relatively few large-scale cross comparator studies examining differences in efficacy between the ASMs used in focal-onset epilepsy. The SANAD (Standard And New Antiepileptic Drugs) study compared a number of different agents in 2007.[11] A Cochrane analysis published in 2017 concluded that levetiracetam likely had similar efficacy and tolerability to lamotrigine. Hence carbamazepine, lamotrigine, and levetiracetam are often considered first line. Alternative ASMs described above have proven effectiveness typically as adjuncts in the treatment of drug-resistant focal epilepsy but there are minimal data to support selection based on efficacy from head-to-head trials.

ASM selection following first-line therapies is predominantly guided by patient demographics, comorbidities, and the varying side effect profiles of individual drugs.

Key study

The SANAD study (2007)[11] was a large pragmatic unblinded randomized controlled trial (RCT), based in the UK. It evaluated the effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate in focal-onset epilepsy. Key findings were that lamotrigine had a longer time to treatment failure than all alternatives, except for oxcarbazepine, and that. Carbamazepine was significantly better than most alternative ASMs in achieving remission at 12 months, although statistically, the advantage with respect to lamotrigine was not significant. The conclusions from this study were that lamotrigine and carbamazepine have similar efficacy, but that lamotrigine is better tolerated.

Generalized seizures

Absence seizures

Typical absence seizures are short episodes of loss of consciousness, usually with preserved muscle tone and minimal motor activity. *De novo* absence seizures beginning in adulthood are rare, and similar symptoms, if epileptic in origin, are more likely to be caused by focal seizures with impaired awareness. Atypical variants can occur where a degree of awareness is preserved.

Treatment

- *First line*: ethosuximide (less commonly used in adults), levetiracetam, or valproate (see p. 33 discussion on valproate use in <55-year-olds)).
- *Second line*: lamotrigine.
- *Third line*: clobazam, clonazepam, phenobarbital, topiramate, or zonisamide.
- Drugs to avoid (may worsen seizures): carbamazepine, eslicarbazepine acetate, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin.

Evidence base

There are few studies on the use of ethosuximide in adults with absence seizures and most of the evidence for use is based on childhood studies. A large double-blind RCT conducted in the USA in 2010 compared ethosuximide, valproate, and lamotrigine in the treatment of childhood absence epilepsy.[12] The study's key findings were:

1. At 16 weeks, the freedom-from-failure rates were higher for valproate and ethosuximide than lamotrigine.
2. Tolerance was similar for all three drugs.
3. Attentional dysfunction was more common with valproate than ethosuximide (49% vs. 33%).

Tonic–clonic seizures

These are classic convulsive seizures. The tonic phase usually lasts for ~20s and involves sustained muscular contraction with loss of consciousness. The clonic phase involves convulsive jerks of all four limbs and may be associated with respiratory arrest. Although a rare event, sudden unexpected death in epilepsy (SUDEP) is far more common in patients with uncontrolled generalized tonic–clonic seizures and hence aggressive treatment of these seizures is recommended.

Treatment

- *First line*: lamotrigine, levetiracetam, topiramate or valproate (see p. 33 discussion on valproate use in <55-year-olds).
- *Second line*: acetazolamide, brivaracetam, carbamazepine, clobazam, clonazepam, oxcarbazepine, perampanel, phenobarbital, or phenytoin.
- *Drugs to avoid*: These are guided by other seizure types present in an individual patient.

Evidence base

A large meta-analysis incorporating eight Cochrane reviews and data from the SANAD study (the second arm of the SANAD study investigated the effectiveness of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy[13]) concluded that valproate performed significantly better than carbamazepine, topiramate, and phenobarbital. There was a non-significant trend suggesting that valproate had a better outcome than lamotrigine, and further analysis of secondary outcomes suggested that 12-month remission levels and time to first seizure were significantly improved with valproate vs. lamotrigine. There was insufficient data to compare valproate with phenytoin; however, it was felt phenytoin had a worse side effect profile.

Myoclonic seizures

Myoclonic movements are brief contractions of muscles or muscle groups. These can be singular or repetitive. They are subdivided depending upon their likely anatomical origin into cortical, subcortical, spinal, segmental, and peripheral. If their aetiology is cortical then they are termed myoclonic seizures. The management of these is discussed below (for management of other myoclonic movements see hyperkinetic movement disorders pp. 200–201). Myoclonic seizures are often short-lived, with little or no post-ictal state.

Treatment

- *First line*: levetiracetam (preferred in women of childbearing potential), topiramate (avoid in women of childbearing potential) or valproate (see p. 33 discussion on valproate use in <55-year-olds).
- *Second line*: brivaracetam, clobazam, clonazepam, piracetam, or zonisamide.
- *Drugs which can exacerbate myoclonic seizures*: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin.

Evidence base

The SANAD study is one of the most important sources of evidence regarding the treatment of juvenile myoclonic epilepsy and isolated myoclonic seizures; however, it did not distinguish juvenile myoclonic epilepsy from other idiopathic generalized epilepsies.[13] There is little high-quality evidence looking specifically at first-line drugs for the treatment of myoclonic epilepsy syndromes.

Tonic and atonic seizures

Tonic seizures are sustained muscular contractions without a clonic phase. They are often associated with classical EEG patterns and more typical of patients with severe learning disability or diffuse cerebral damage. They are commonly present as part of Lennox–Gastaut syndrome (LGS). Atonic seizures are characterized by loss of postural control. This can occur either suddenly in the form of a drop/astatic attack where individuals fall to the floor, or slowly where there may be a progressive loss of tone in the limbs and neck. The astatic attacks are often short-lasting with a swift recovery.

Treatment

- *First line*: lamotrigine, levetiracetam, or valproate (see p. 33 discussion on valproate use in <55-year-olds).
- *Second line*: acetazolamide, brivaracetam, clobazam, clonazepam, phenobarbital, rufinamide, or topiramate.
- *Drugs which may exacerbate tonic and atonic seizures*: carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin.

Evidence base

Most of the evidence is extrapolated from knowledge of ASM effectiveness in other generalized epilepsy syndromes, in combination with expert opinion.

Epilepsy syndromes

ASM selection in individual epilepsy syndromes mostly depends upon the different seizure types displayed by the individual patient. For example, in the syndrome epilepsy with generalized tonic–clonic seizures alone, treatment recommendations are the same as for treatment of generalized seizures.

In more complex epilepsy syndromes where there is a mixture of seizure types, e.g. juvenile myoclonic epilepsy, which might involve both myoclonic seizures and generalized tonic–clonic seizures, care must be taken to avoid exacerbating one seizure type whilst treating another. Carbamazepine, gabapentin, and several other drugs (see above in the myoclonic seizure section) may be effective in the treatment of primary generalized seizures but can exacerbate myoclonic seizures. Even in generalized epilepsies of presumed genetic origin characterized by generalized tonic–clonic seizures alone, initiation of these medications may result in the de novo appearance of new seizure types as a side effect and this possibility should be considered when choosing an ASM.

Given the restricted licensing of newly available medications for Dravet syndrome and Lennox–Gastaut Syndrome (LGS) these will be discussed in more detail:

Dravet syndrome

Dravet syndrome is a rare (~1 in 250 children with epilepsy) childhood-onset epilepsy syndrome that usually presents in the first year of life with generalized clonic or focal clonic seizures. These are typically prolonged and can be triggered by febrile illnesses. Atypical absence and myoclonic seizures develop over the next few years. These children have significant developmental delay and learning difficulties because of an epileptic and developmental encephalopathy. Seizure frequency tends to reduce in adulthood, but they are often still clinically problematic. SCN1A mutations account for up to 80% of patients, the majority of which have arisen 'de novo'.

Seizures can be resistant to ASM therapy and often manifest as prolonged episodes of status epilepticus. Multiple ASMs are usually required, combined with an emergency health care plan with rescue medications for rapid management of prolonged seizures. ASMs which act on sodium channels are relatively contraindicated as they can make seizure control worse. Several ASMs are felt to have synergistic effects on seizure control, and this is reflected in their licence. Stiripentol is licensed for use only when co-prescribed with clobazam and valproate, similarly Epidiolex (cannabidiol) is licensed for use when co-prescribed with clobazam.

Fenfluramine was approved for use by the FDA in June 2020 for the treatment of Dravet syndrome. It is an agent originally used as an appetite suppressant before being withdrawn from the market in the 1990s, due to its association with cardiac fibrosis and pulmonary hypertension. Several RCTs were published recently wherein the higher dosed groups demonstrated a 50 and 70% reduction in seizure frequency, depending on whether patients were taking stiripentol or not (50% if patients were also taking stiripentol and 70% if they were not) (see individual drug monograph for further information). Neither of the two studies or the open label extension study demonstrated clinical or echocardiographic evidence of valvular heart disease or pulmonary hypertension. Given its clear efficacy this ASM may be a very useful agent in the management of Dravet syndrome.

Treatment

- *First line*: levetiracetam, or topiramate.
- *Second line*: clobazam, or stiripentol.
- *Third line*: cannabidiol, clonazepam, fenfluramine, ketogenic diet, valproate (see p. 33 discussion on valproate use in <55-year-olds) or zonisamide.
- Drugs which may exacerbate absence and myoclonic seizures: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, tiagabine, and vigabatrin.

Evidence base

Use of most agents in Dravet syndrome is predominantly based on expert opinion and non-randomized studies. Use of the newer agents stiripentol and cannabidiol are supported by RCTs, which demonstrated a reduction in seizure frequency when these ASMs are used as an adjunct to first line medications. Overall level of functioning also improved suggesting better seizure control improves the background encephalopathy.

Lennox–Gastaut syndrome

LGS is a severe childhood-onset epileptic and developmental encephalopathy accounting for 1–10% of childhood-onset epilepsy. It typically starts between 2–5 years of age. It is characterized by a combination of seizure types which can include tonic and/or atonic seizures resulting in sudden drop attacks, as well as atypical absence seizures, and less frequently myoclonic, focal, and tonic–clonic seizures. There is usually concurrent intellectual disability and a characteristic EEG pattern. Seizures can progress over time and prolonged episodes of status epilepticus as well as clusters of seizures are common. Typical aetiologies include structural abnormalities such as cortical malformations and perinatal hypoxic-ischaemic injury, as well as several genetic abnormalities.

Seizures can be resistant to ASM therapy. As for Dravet syndrome, optimal management frequently requires multiple ASMs combined with an emergency health care plan for rapid control of prolonged seizures.

Treatment

- *First line*: clobazam, lamotrigine (can exacerbate myoclonic seizures) or topiramate (avoid in women of childbearing potential).
- *Second line*: cannabidiol, or rufinamide.
- *Third line*: felbamate, levetiracetam, perampanel, valproate (see p. 33 discussion on valproate use in <55-year-olds) or zonisamide.
- *Drugs which may exacerbate absence and myoclonic seizures*: carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin.

Evidence base

Use of most agents in LGS is based on expert opinion and small RCTs. A 2013 Cochrane review concluded that optimum treatment strategies remain uncertain as no one drug appeared highly efficacious.[14] Valproate is typically considered first line based on expert opinion and an early observational study. Use of cannabidiol, clobazam, felbamate, lamotrigine, rufinamide, and topiramate is supported by small RCTs.

A trial investigating the use of fenfluramine for LGS was completed in 2020. Its use led to a >50% reduction in monthly drop seizures in 25% of patients, compared to 10% with placebo. It is not yet licensed for this indication (see drug monograph for further information).

Antiseizure medications (ASMs) in women of childbearing potential

Pregnancy

Pregnancy typically has little impact on the frequency of seizures for most women with epilepsy. In a minority, usually those with severe epilepsy, seizures worsen (17%), while in others seizures may decrease or cease altogether (16%). Seizure frequency may change due to fluctuations in plasma levels of ASMs caused by changes in gastric motility, plasma proteins, plasma volume, hepatic, and renal function and volume of distribution. In addition, vomiting, stress, sleep deprivation, and inappropriate dose reductions by doctors, or by patients themselves may contribute. The risks of poorly controlled epilepsy in pregnancy include trauma to the feto-placental unit during convulsions, as well as a 50% fetal, and 30% maternal, risk of mortality if status epilepticus develops. Hence, in some instances where plasma ASM levels drop in pregnancy, ASM doses may have to be increased temporarily, although there is minimal evidence this has a significant clinical impact.

Labour

ASMs should be given as normal during labour; if this is not possible, an alternative method of enteral/parenteral administration should be used. 1–2% of women with epilepsy will have tonic–clonic convulsions during delivery, hence patients with epilepsy should ideally give birth in hospital, with continuous fetal monitoring. In the minority of patients deemed at high risk of seizures, prophylaxis with 10–20 mg of clobazam should be considered in the early stages of labour. If the risks are significant, then a Caesarean section may be indicated. Prolonged seizures and status epilepticus during pregnancy should be treated as for other adults. Neonates are very susceptible to medication related respiratory depression.

Effects on the fetus of antiseizure medication use during pregnancy

Major congenital malformations

ASM use during pregnancy can be associated with teratogenicity. This has been confirmed in several human observational studies for many of the older drugs. Animal studies have suggested that several newer ASMs may also have teratogenic potential. The background proportion of teratogenicity in the normal population is ~2% whereas congenital malformations occur in 4–7% of patients taking ASMs (see Table 3.1) and 3.5% of patients with epilepsy not on ASMs.[15] The likelihood of congenital malformations is higher with high doses of ASMs, multiple ASMs, and specific ASMs, e.g. valproate.

Fetal anticonvulsant syndromes and reduced cognitive function.

Fetal carbamazepine, phenobarbital, phenytoin, primidone, and valproate syndromes have all been described. The clinical pictures vary and include patterns of dysmorphism, e.g. growth delay, finger hypoplasia, and even an increased risk of neuroblastoma with phenytoin use. The link between these syndromes and ASMs is controversial as the features described have

Table 3.1 The risk ratio of major congenital malformations with ASM monotherapy in pregnancy

ASM	Compared to children born to women without epilepsy (RR, 95% CI)
Carbamazepine	2.01, 1.20–3.36
Gabapentin	No increased risk
Lamotrigine	No increased risk
Levetiracetam	No increased risk
Phenytoin	2.38, 1.12–5.03
Topiramate	3.69, 1.36–10.07
Valproate	5.69, 3.33–9.73
Zonisamide	No increased risk

Data from Weston J *et al.*, 2016.[15]

a large degree of overlap with the normal population. A large study conducted in 2009 suggested that children exposed to valproate *in utero* had an intelligence quotient (IQ) 9 points lower than children who were exposed to other ASMs, e.g. lamotrigine.

Valproate

In the UK, use of valproate in women was significantly restricted by a 2018 guideline prepared by the Medicines and Healthcare products Regulatory Agency, an executive agency of the Department of Health and Social Care. This was based on data suggesting that as many as 10% of children born to women taking valproate had a birth defect and up to 40% of children developed subtle developmental problems, such as lower IQs and poor memory, speech and language skills. The MHRA state that valproate should be avoided in women of childbearing potential. If it is used a 'Pregnancy prevention programme' should be instituted which requires a user-independent form of contraception to be used, e.g. an intrauterine device (IUD) or implant. The need for valproate needs to be continually reviewed and there should be an annual written consent. More recent CHM recommendations have advocated that stricter control is necessary, including limiting use in both men and women <55 years old and that two specialists independently review and document that no other effective or tolerated treatment is an option.[10]

In the USA the FDA has advised against valproate prescription for women of childbearing age unless the drug is essential for the management of their medical condition.

Management strategies

Effective early (pre-conception) communication of the potential additional risks of ASMs in pregnancy is key, as many teratogenic effects occur in the first trimester.

Options include:

- withdrawal of ASMs prior to conception. Typically, only considered if the epilepsy has been in remission for several years. This may mean that pregnancy is delayed for a few years, so that ASMs can be reduced and stopped safely. Ideally medication changes should be completed 12 months pre-conception. In women who have been seizure-free for nine months prior to pregnancy ~90% will not have any breakthrough seizures during the pregnancy.
- continuation of ASMs throughout pregnancy.
- discontinuation of ASMs in the first trimester, restarting in the second.
- aiming for monotherapy at the lowest doses possible, and avoidance of valproate.

If a pre-conception review was not possible, an in-depth discussion is required to consider whether to continue ASMs in pregnancy. If the decision is to stop treatment, ASMs should be tapered slowly to avoid rebound seizures.

If ASMs are continued during pregnancy:

- a drug plasma level can be taken before or during early pregnancy to establish the effective dose for seizure control in that individual.
- plasma levels can then be monitored, and doses adjusted throughout pregnancy to ensure continuing therapeutic plasma levels; this

particularly applies to lamotrigine and levetiracetam, (to a lesser extent, carbamazepine, phenytoin, and phenobarbital) whose levels can change dramatically during pregnancy (see individual drug monographs).
- monthly plasma levels can be considered with lamotrigine.

Harmful effects of ASMs during pregnancy can be minimized by:
1. Folic acid while patients during attempted conception and the first trimester to reduce the risk of neural tube defects. The recommended dose varies depending on the country and a patient's individual risks. UK national guidance recommends 5 mg/day, the American Academy of Neurology (AAN) at least 0.4 mg/day, although doctors will often prescribe more (up to 4 mg/day) if there is a higher risk of malformations, such as a family history of neural tube defects or if the patient is taking higher risk or multiple ASMs.
2. Specific screening regimes for fetal abnormalities.
3. Neonatal vitamin K injections if the ASMs are enzyme-inducing, to reduce the risk of haemorrhagic disease of the new-born.

Contraception

Many of the commonly used ASMs increase the metabolism of the oral contraceptive pill, thereby increasing the risk of unplanned pregnancy (Table 3.2). If enzyme-inducing ASMs are used, then hormonal methods of contraception may not be reliable and barrier methods and coil devices should be considered. If oral contraceptives are the only acceptable option,

Table 3.2 The effects of ASMs on the contraceptive pill

No effect	Reduced plasma levels	Not known
Acetazolamide	Carbamazepine	Cannabidiol
Benzodiazepines*	Cenobamate	Fenfluramine
Brivaracetam	Eslicarbazepine acetate	Paraldehyde
Ethosuximide	Felbamate	Stiripentol
Gabapentin	Fosphenytoin	
Lacosamide	Lamotrigine	
Levetiracetam	Oxcarbazepine (typically at higher doses)	
Methsuximide	Perampanel	
Piracetam	Phenobarbital	
Pregabalin	Phenytoin	
Tiagabine	Primidone	
Valproate	Rufinamide	
Vigabatrin	Topiramate (typically at >200 mg/day)	
Zonisamide		

*Including: clobazam, clonazepam, diazepam, lorazepam, and midazolam then high-strength formulations should be used. In addition, higher doses of the morning-after pill may be required.

Plasma lamotrigine levels decrease significantly when combined oral contraceptives (COCs) are co-prescribed. This can lead to worsening of seizure control in patients already established on lamotrigine or cyclical toxicity during the 7-day off-period with COCs.

How to withdraw antiseizure medications

Risks and benefits of stopping antiseizure medications

ASMs have side effects, drug interactions, and the potential for teratogenicity. Once seizure control is achieved, discontinuing ASMs is attractive for many patients. However, stopping ASMs increases the likelihood of recurrent seizures with associated risks of physical injury and death (for generalised tonic-clonic seizures (GTCS)) and societal implications such as on driving and employment. Twenty-five per cent of patients attempting to withdraw will relapse within one year, and ~30% will relapse within two years. In patients who had been seizure-free for two years, ~60% will remain seizure-free two years after stopping treatment, compared to 78% of patients who remain on medication. Of those who relapse, 8% will not regain seizure control, even if the original ASMs are reinstated.[16]

Timing of antiseizure medication withdrawal

This is a matter of much debate but little evidence. A meta-analysis in children showed that seizure recurrence was less likely if patients were seizure-free for two years prior to stopping ASMs. There have been no effective trials in adults. Expert consensus is that ASM withdrawal in adults is also safer after two years of seizure freedom. In patients who have had surgical treatment for epilepsy, expert consensus again suggests it is safer to withdraw gradually after two years of treatment, although often long-term monotherapy is required.

Procedure of antiseizure medication withdrawal

ASMs should be tapered, rather than abruptly stopped, to reduce the risk of seizure recurrence and status epilepticus. There is little evidence as to exactly how fast these medications should be withdrawn. The advice is to reduce ASMs sequentially, the speed of which depends on:

1. patient factors, e.g. the epilepsy type or the nature and degree of drug side effects experienced by the individual patient.
2. medication factors, e.g. dose, half-life, and duration of treatment.

As a rule, if seizures recur, 50% occur in the withdrawal period, 25% in the subsequent year.

If seizures occur during drug reduction, then the ASM should be increased to the last dosage which successfully controlled the epilepsy.

Status epilepticus

Status epilepticus is a life-threatening neurological emergency defined as ‘a condition resulting from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures’.[17] It can have long-term consequences including neuronal death, neuronal injury, and alteration of neuronal networks. The duration at which seizures are considered prolonged and where the risk of the long-term consequences arises varies depending on the seizure type. In the context of generalized tonic–clonic seizures this is 5 min and 30 min, respectively, based on animal models. The mortality rate is 2% in the healthy adult, and can be as high as 30% in the context of hypoxic brain injury, stroke, drug toxicity, comorbidity, central nervous system (CNS) infection, prolonged status, and delayed effective treatment.

Investigation of status epilepticus

Preliminary investigation is aimed at identifying the most likely causes (see Table 3.3):

- full physical assessment.
- blood screen: glucose, full blood count (FBC), C-reactive protein (CRP), liver and renal function tests, blood gases, calcium, magnesium, coagulation studies, screen for alcohol and drugs of abuse, and ASM levels if appropriate.
- chest X-ray (CXR), neuroimaging, lumbar puncture, and EEG to be considered.

Intensive monitoring of physical and neurological observations, biochemistry, and EEG is required if status is sustained. Metabolic compromise and hypoxia are common consequences of prolonged seizures, and both may

Table 3.3 Aetiology of status epilepticus in adults

	Aetiology	Percentage
Patient with a diagnosis of epilepsy	Low plasma levels of ASMs (e.g. non-adherence/omission)	~30%
	Drug-resistant epilepsy	6%
Individuals without a previous diagnosis of epilepsy	Alcohol- and drug-related	~25%
	CNS infection	8%
	Drug-resistant epilepsy	6%
	Trauma	6%
	Neoplastic space-occupying lesion	6%
	Acute stroke	6%
	Metabolic causes	4%
	Hypoxia	4%
Miscellaneous		6%

Based on Delorenzo RJ *et al.*, 1999[18] and Bleck T *et al.*, 2010.[19]

lower the chances of seizure termination and increase the risk of neuronal cell death.

Management of status epilepticus

Early and aggressive treatment of status epilepticus is essential and should address the following three aspects in parallel (see Fig. 3.3):

1. resuscitation and cardiorespiratory support.
2. identification of the underlying cause of the seizure.
3. ASM therapy.

The following algorithm is based on the American Epilepsy Society guideline[20] and the NICE Epilepsies in children, young people, and adults. Guideline CG217,[8] with updates from recent trials.

Initial therapy (5–20 min)

Benzodiazepines: the drug selected depends on local availability and protocols, and the ability to secure IV access

In the absence of IV access buccal midazolam 10 mg, IM midazolam 10 mg or rectal diazepam 10–20 mg.

If IV access is available IV diazepam 5–10 mg or lorazepam 4 mg.

The dose should be repeated after 10 min if the seizure has not stopped. IV diazepam or lorazepam alone in early status will terminate 60–80% and 60–90% of seizures, respectively.

Replace normal ASMs and correct obvious abnormalities. Omission of ASMs in patients with epilepsy can contribute to over 25% of prolonged seizures. Regular ASMs should be re-established as soon as possible. Loading doses of some drugs may be required, depending on how long the ASMs have been omitted. In addition, obvious precipitants should be

Stage of status epilepticus	Resuscitation and cardiorespiratory support	Identification of the underlying cause	Anti-epileptic therapy
Initial Therapy 5–20 mins	Secure airway, give oxygen, and resuscitate	Physical examination and blood screen	Benzodiazepines
Second Therapy 20–40 mins	Regular cardiovascular monitoring	Consider CXR, CT head, ECG and lumbar puncture as required	Fosphenytoin, levetiracetam, Phenytoin or sodium valproate
Third therapy >40 mins	Consider ITU level care	Consider need for continuous EEG and ICP monitoring	General anaesthesia

Fig. 3.3 Flow diagram summarizing the management of status epilepticus.

corrected, e.g. alcohol withdrawal, electrolyte abnormalities, hypertension, and hypoglycaemia.

Second Therapy (20–40 min, established status)

Options include:

- levetiracetam: 60 mg/kg (max dose 4500 mg) by IV infusion over 10 min; or
- phenytoin: 20 mg/kg by IV infusion at a rate of 50 mg/min; or
- fosphenytoin: 20 mg phenytoin equivalents/kg (max 1500 mg phenytoin equivalents (PE)) by IV infusion over 10 min; or
- valproate: 40 mg/kg (max 3000 mg) by IV infusion over 10 min; or
- phenobarbital: 15 mg/kg by IV infusion at a rate of 100 mg/min.

Regular blood pressure (BP) and ECG monitoring should be used in established status, both to monitor for complications of drug therapy and for complications of status itself.

Third therapy (>40 min, refractory status)

An estimated 30% of prolonged seizures progress to refractory status. At this point, a therapeutic coma is typically induced with a general anaesthetic (GA) to terminate seizure activity, aiming for burst suppression on EEG. This should be achieved for at least 12 h, before the GA can be slowly weaned over at least another 12 h. If seizures recur, the cycle is repeated. The commonest agents used are propofol and midazolam. Thiopental and pentobarbital are barbiturate alternatives. Propofol should not be used for >5 days, as ‘propofol infusion syndrome’ can cause life-threatening liver failure and rhabdomyolysis.

Options include:

- propofol 2 mg/kg bolus by IV injection at a rate of 20–f every 10 s followed by infusion of 2–10 mg/kg/h.
- midazolam: 0.1–0.2 mg/kg bolus by IV injection, followed by an infusion at 0.05–0.5 mg/kg/h.
- thiopental: 75–125 mg bolus (2.5%, 25 mg/mL) (3–5 mg/kg bolus in individuals <18 years), given as a slow IV injection followed by slow IV injection at 8 mg/kg/h.

Evidence base

Initial therapy

Systematic reviews have shown IV lorazepam is associated with a significant reduction in the risk of seizure continuation and requirement for ventilatory support when compared to diazepam (and compared to phenytoin). Diazepam may work slightly faster than lorazepam because it is distributed more rapidly throughout the cerebrum, but its anticonvulsant effect is comparatively short-lived, (~20 min, compared to 6 h with lorazepam) because of rapid redistribution into fat and consequent fall in plasma levels. The RAMPART study, a pre-hospital study comparing IM midazolam with IV lorazepam confirmed that IM midazolam was at least as effective as IV lorazepam for prehospital cessation, as the slower rate of absorption from IM injection vs. IV injection was offset by the time taken to site intra-venous access (the median time to treatment administration being 4.8 min in the IV lorazepam group vs. 1.2 min in the IM midazolam group).[21]

Second Therapy

The ESETT trial (Established status epilepticus treatment trial), compared the safety and efficacy of fosphenytoin, levetiracetam, and sodium valproate in benzodiazepine-resistant established status by age group.[22] All 3 drugs terminated status in ~50% of cases. There were no significant differences in efficacy or safety outcomes in the adult group.

- Phenytoin is historically the most widely used agent. It will terminate >50% of benzodiazepine-resistant seizures. Fosphenytoin is a phenytoin prodrug, which can be infused faster than phenytoin and, unlike phenytoin, is not associated with purple glove syndrome.
- Phenobarbital has comparable efficacy to phenytoin, terminating ~60% of seizures unresponsive to benzodiazepines. It is often used second line after other ASMs, due to perceived increased risks of respiratory depression and sedation. In fact, several randomized controlled studies have shown little difference in side effect profile when used in status.

Third Therapy

The evidence base for treatment of refractory status epilepticus is limited. A Cochrane review on the subject concluded that, for propofol and thiopental, there was insufficient evidence to suggest either drug was more effective.[23] The only significant difference noted was a need to provide prolonged mechanical ventilation when thiopental was used.

Super-refractory status epilepticus

If propofol-, midazolam-, or barbiturate-induced coma fail to induce burst suppression, then status enters a stage which some experts term 'super-refractory status epilepticus'. This may occur in up to 15% of patients hospitalized with status. It is defined as status lasting longer than, or recurring after, 24 h of anaesthetic-induced coma. The evidence base for treatment in this subgroup is minimal.[24]

Alternative GAs, such as lidocaine, ketamine, etomidate, or clomethiazole can be trialled. Hypothermia, corticosteroids, immunotherapy, the ketogenic diet, and neurosurgery are also potential options.

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Chapter 4

Cerebrovascular disease

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Introduction

The World Health Organization (WHO) defines stroke as a syndrome characterized by ‘rapidly developing clinical signs of focal (or, rarely, global, e.g. coma) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of presumed vascular origin’.[1–3] The key factors are the sudden onset of a focal neurological syndrome (e.g. hemiparesis, dysphasia, visual field loss, etc.); non-focal syndromes (such as loss of consciousness) are only rarely due to stroke. Neuroimaging is increasingly used to confirm the exact pattern of brain tissue injury.

In modern practice, clinicians are unable to wait 24 h to diagnose acute stroke, as strategies aimed at improving perfusion need to be implemented as soon as possible following the onset of symptoms (‘*Time is brain*’).[3] Despite dramatic improvements in the treatment of acute stroke and in secondary stroke prevention over the last decade, mortality remains 10–20% at 1 month.[4] Moreover, 37% of survivors remain dependent for all their daily functions at 1 year.[5] This makes stroke both the second commonest cause of death worldwide (after ischaemic heart disease) and the leading cause of neurological disability worldwide.[1–3]

Classification

- Stroke can be classified as ischaemic (~85% of all strokes) or haemorrhagic (mainly intracerebral and subarachnoid; ~15%).[1–3] Intracerebral haemorrhage (ICH) may be traumatic or non-traumatic (spontaneous).[6] Spontaneous ICH can be further subdivided into ‘primary’ or secondary—the former term refers to ICH arising from small-vessel pathology, most often hypertensive arteriopathy and cerebral amyloid angiopathy (CAA), and the latter arising from a variety of predominantly structural abnormalities, including arteriovenous malformations and tumours. However, the term ‘primary’ is not recommended as it is imprecise and discourages adequate investigation and classification of ICH.

Ischaemic stroke

Ischaemic stroke is characterized by an acute onset neurological deficit, resulting from cessation of blood flow to a focal area of the brain. The area of the brain affected corresponds to the vascular territory of an occluded artery (see Table 4.1). The commonest mechanisms of ischaemic stroke are cardioembolic, large artery disease (athero-thromboembolism), and small-vessel disease (see Fig. 4.1).[1,2]

1. Large artery disease is primarily atherosclerosis affecting the cervical carotid and vertebral arteries, as well as the intracranial arteries. Thromboemboli can arise from these lesions and significant stenosis can also diminish downstream perfusion. In addition to atherosclerosis, other pathologies such as dissections and vasculitis can also cause large artery lesions.

Table 4.1 Expected neurological deficits following ischaemia of different cerebral artery vascular territories

Artery	Deficit of stroke
Anterior cerebral artery	Leg > arm and face (motor and sensory loss) Behavioural change (abulia)
Middle cerebral artery	Face, arm > leg (motor and sensory loss) Speech (left), neglect, homonymous hemianopia
Posterior cerebral artery	Homonymous hemianopia, cortical blindness if bilateral (rare)

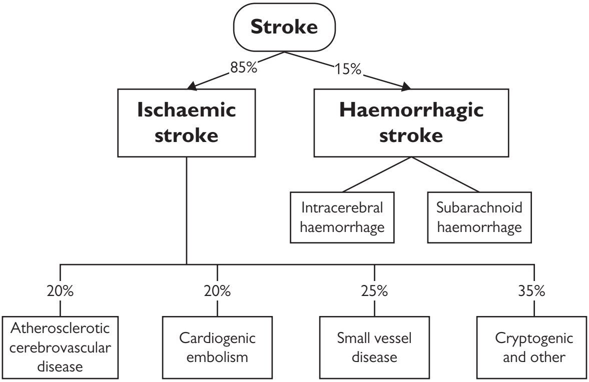
Stroke
85%
15%
Ischaemic stroke
Haemorrhagic stroke
Intracerebral haemorrhage
Subarachnoid haemorrhage
20%
20%
25%
35%
Atherosclerotic cerebrovascular disease
Cardiogenic embolism
Small vessel disease
Cryptogenic and other

Fig. 4.1 Causes of stroke.

2. Cardioembolic strokes arise from embolization of cardiac thrombi, most commonly in the context of atrial fibrillation (AF) or ischaemic heart disease. Bacterial endocarditis, prosthetic heart valves, and atrial myxomas are other possible sources of emboli. Paradoxical embolism through a patent foramen ovale is also a consideration.
3. Small-vessel disease (i.e. small subcortical infarcts associated with lacunar syndromes) are secondary to intrinsic pathology of small cerebral perforating end-arteries which supply the subcortical structures (basal ganglia, thalamus, internal capsule, and brainstem), and not the cerebral cortex. *In situ* disease of the small vessels, including microatheroma and lipohyalinosis, most commonly occurs as a consequence of hypertensive arteriopathy. A history of hypertension is present in ~80% of these patients, although this may be an overestimate, as hypertension is sometimes required in the definition of the stroke type.[7]

The most important risk factors for ischaemic stroke are age and hypertension, but smoking, diabetes, hyperlipidaemia, AF, coronary artery disease, family history of stroke, and personal history of previous stroke and TIA are also important.[1,2] In younger patients, oral contraceptive use, hypercoagulable states, vasoconstrictive and other recreational drug use, craniocervical arterial dissection, polycythaemia, and sickle-cell disease should be considered.[8]

Pathophysiology

Acute arterial occlusion to an area of the brain results in a spectrum of ischaemic damage to brain tissue, which depends on the size of the occluded vessel, the duration of occlusion, and the degree of collateral blood supply to areas of the brain within the territory of the occluded vessel. The area of affected brain comprises two distinct zones: the ischaemic core and ischaemic penumbra.[9] The core is a region of the brain with such low blood supply that cell death occurs within minutes of the ischaemic insult. The penumbra is a variably sized area where blood supply from collateral vessels, or from the partially occluded affected vessel, is sufficient to maintain cellular survival for up to several hours to days. Cells within the penumbra are deprived of oxygen and other elements essential for cellular metabolism, and hence lose many of the cellular protective mechanisms to further insults. Therefore, this area is very vulnerable to necrotic cell death from small changes in oxygen level, BP, and blood glucose levels, as well as other metabolic parameters.

The focus of early treatment is to facilitate recanalization (e.g. with fibrinolytics or endovascular clot removal devices) and to optimize the physiology of cells within the ischaemic penumbra by regulating important physiological parameters and rapidly treating complications, such as infection and seizures, which place an added metabolic strain on cerebral neurons.

Haemorrhagic stroke

- Intracranial haemorrhage refers to any bleeding within the skull, including the subdural, extradural, subarachnoid, and intracerebral compartments. Conventionally the term ‘haemorrhagic stroke’ refers to non-traumatic ICH (within the brain substance), or sometimes both intracerebral and subarachnoid haemorrhage.[6] The commonest cause, accounting for about 80% of all of spontaneous (non-traumatic) ICH, is cerebral small-vessel disease, secondary to deep perforator arteriopathy (also termed arteriolosclerosis or hypertensive arteriopathy), CAA, or both.[10] ICH accounts for ~10–15% of all strokes in developed countries and carries a 30-day mortality of 40–50%, mostly within the first 2 days. The clinical presentation depends upon the location and size of the haemorrhage and whether there is extension into the ventricles, secondary vasospasm, herniation, and/or hydrocephalus. Subarachnoid haemorrhage (SAH) is discussed in more detail in Subarachnoid haemorrhage, p. 64.

Management of acute stroke: overview

The emphasis of early management is resuscitation and supportive measures, combined with rapid neuroimaging to differentiate ischaemic from haemorrhagic stroke and allow decisions to be made regarding thrombolysis, thrombectomy, and other hyperacute interventions.[3]

1. Ensure a patent airway to avoid aspiration and hypoxia.
2. Arrange urgent neuroimaging to assess for intracranial haemorrhage and look for signs of early or established infarction. Computed tomography (CT) is usually the first-line imaging study because of its speed, availability, and ability to detect acute blood. MRI is much more sensitive to cerebral ischaemia in the hyperacute phase but, in many countries, is not yet as readily available.
3. Monitor blood glucose, aiming for levels between 4 and 11 mmol/L (insulin sliding scales can be used, if necessary). Occasionally, hypoglycaemia can mimic acute stroke.

If haemorrhagic stroke is excluded:

1. Thrombolytic therapy may be administered if the patient is seen within 4.5 h of last known well and there are no contraindications.
2. Antiplatelet therapy as soon as possible if outside of the thrombolytic window, or in 24–48 h if thrombolysis has been given.

The effects of variations in BP differ between stroke subtypes. The penumbra has limited cerebral perfusion and hence theoretically may not tolerate acute drops in systemic BP; however, if the BP is too high, the chance of a haemorrhagic conversion may be increased.

In haemorrhagic stroke, elevated BP is associated with haematoma expansion, which can be reduced (modestly) by intensive early treatment.

The evidence base and practical guidelines for blood pressure management in different scenarios is discussed further in the individual stroke subtype sections.

Management of blood pressure in acute ischaemic stroke

BP is a dynamic parameter in the early phases of acute stroke. Early trials suggested that acute reduction in BP was associated with poorer outcomes. Subsequent randomized trials have unfortunately failed to help establish a consistent approach to treatment for ischaemic stroke.

BP is monitored, and hypertension treated only if one or more of the following conditions are met:

- systolic persistently >220, diastolic>110, or mean arterial BP >130mmHg.
- hypertensive encephalopathy, acute myocardial infarction (MI), aortic dissection, or severe heart failure is present.
- the patient is to receive thrombolytic therapy, prior to which BP should be maintained below 180/105 mmHg for bolus and 180/110 mmHg for infusion.

General principles of best care are listed below.

1. BP management should be performed in a controlled manner and if required hyperacutely (within the first 24–48 h) is best achieved with easily titrated IV agents.
2. When hypotension is present (systolic BP <120 mmHg or BP significantly lower than premorbid state), the patient should be flat and administration of IV fluids is considered to improve cerebral perfusion. Vasopressors may be considered if hypotension is severe and cannot be corrected by other means.
3. Candidates for thrombolysis who are hypertensive (systolic BP >185/110 mmHg) should be given IV antihypertensives (e.g. labetalol, glyceryl trinitrate (GTN) and nicardipine). If BP remains elevated, boluses can be repeated, or infusions can be started.[11]
4. BP should be maintained below 185/110 mmHg for thrombolysis bolus and below 180/105 mmHg throughout thrombolysis. After thrombolysis, BP should be recorded every 15 min for 2 h, then every 30 min for 6 h, and subsequently every hour for 16 h.
5. In patients with ischaemic stroke not undergoing thrombolysis, there is little evidence to support treatment of hypertension. High BP often spontaneously resolves within the first 24 h. The American Stroke Association recommends only treating elevated BP in the first 24 h if there is malignant hypertension (as defined by BP which is so high that it has caused end-organ damage, e.g. stroke, MI, or renal impairment) or a co-morbidity that requires urgent BP-lowering therapy.[3] This is also the principle used where thrombectomy may be utilized.

Ultimately, a clinician must weigh up a patient's baseline BP, the type of stroke (see p. 49), whether a patient has been thrombolysed and hence is at a higher risk of bleeding, and the degree of extracranial (carotid or vertebrobasilar) artery stenosis (if known) and hence the potential increased risk of cerebral hypoperfusion with sudden drops in BP, among other factors.

Ischaemic stroke and transient ischaemic attack

Management of acute ischaemic stroke

Acute treatment

1. If ischaemic stroke is identified within 4.5 h of the last known well, and there are no contraindications, then thrombolysis— IV alteplase 0.9 mg/kg over 1 h or IV tenecteplase 30–50 mg should be administered.[3]

2. If an ischaemic stroke is identified outside of the thrombolysis window, then antiplatelet therapy should be initiated as soon as possible. Antiplatelets should be held for 24–48 h post-thrombolysis administration.[3]

Antiplatelet therapy

- Dual antiplatelet therapy (DAPT) for 3 weeks (CHANCE) to 3 months (POINT).[12,13] If intracranial atheromatous disease related to stroke is identified, then 3 months DAPT is recommended.[13]
- If not a candidate for DAPT based on inclusion criteria from these trials, then give antiplatelet monotherapy.
- Longer-term antiplatelet therapy: see Secondary prevention following an ischaemic stroke or transient ischaemic attack, p. 58.

Evidence base

Antiplatelet therapy

The 2018 Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (n = 4881, ASA and clopidogrel vs. ASA and placebo) found that starting DAPT within 12 h of the onset of stroke for 90 days reduced the 90-day stroke incidence (4.6% vs. 6.3% (HR 0.72; 95% CI 0.56–0.92; p = 0.01) but increased bleeding risk compared to aspirin therapy alone.[13] It was shown that the primary stroke reduction benefit was seen within the first 30 days of DAPT. The 2013 Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial (n = 5170 Chinese subjects, ASA and clopidogrel vs. ASA and placebo) showed that DAPT vs. ASA alone for 21 days reduced stroke incidence 11.7% vs. 8.2% (HR 0.68; 95% CI 0.57–0.81; p <0.001) without an increase in bleeding risk.[12]

Thrombolysis

For patients with suspected acute ischaemic stroke seen within 3h, and if criteria are met within 4.5 h, several trials have demonstrated improved functional outcome with administration of tissue plasminogen activator (tPA). Until recently the agent of choice was alteplase (rt-tPA), however tenecteplase is gaining greater utilization with strong evidence supporting its efficacy and growing evidence of its superiority compared to alteplase.[14]

For patients treated within 3 h, the initial trials demonstrated an increase in good functional outcome and a non-significant trend towards a 4% decrease in mortality with alteplase. A meta-analysis of RCTs of thrombolytics in acute ischaemic stroke (12 trials, 7012 patients) demonstrated that thrombolysis given within 6 h of stroke significantly increased the probability (4.2%) of being both alive and independent (Modified Rankin Scale (MRS) 0–2) at final follow-up (OR 1.17, 95% CI 1.06–1.29; p = 0.001). The analysis confirmed that the greatest benefit in neurological outcome was demonstrated in patients treated within 0–3 h (MRS 0–2, 365/896 [40.7%] vs. 280/883 [31.7%], OR 1.53, 95% CI 1.26–1.86; p <0.0001). Mortality within 7 days was increased by 2.5% in those who were thrombolysed (primarily accounted for by intracranial haemorrhage). However, by final follow-up, this excess mortality was no longer significant, indicating overall benefit from treatment. The benefit of thrombolysis was also seen in those >80 years old.[15]

A systematic review of 6 RCTs comparing the effect of tenectaplase (10–40 mg) to alteplase (90 mg) including 1675 stroke patients concluded that tenecteplase was just as good, and in some cases better, than alteplase with regard to the outcomes of post thrombolytic bleeding, functional outcome at 90 days as measured by the MRS, and recanalization/reperfusion rates following thrombectomy.[14]

Thrombectomy

Since the publication of 5 RCTs in 2015, endovascular therapy for acute ischaemic stroke has become the standard of stroke care for large vessel occlusion (LVO) strokes. This has led to the use of several novel antithrombotic agents (e.g. cangrelor and ticagrelor) intra-operatively as well as use of antiplatelet therapy to prevent stent thrombosis.

Presently, thrombectomy for LVO stroke has been shown to be efficacious up to 24 h after onset of symptoms with favourable perfusion imaging.[16]

Surgical interventions

Decompressive hemicraniectomy should be strongly considered in the ~10% of ischaemic stroke patients who have a 'malignant' middle cerebral artery syndrome (characterized by rapid deterioration in neurological function due to the rapid rise in intracranial pressure (ICP) with cerebral oedema, following a large infarct of the MCA territory). Surgery should be performed within 48 h of symptom onset for best results. The randomized trial evidence for benefit is most convincing in individuals <60 years, but some older patients can also benefit (DESTINY 2 trial).[17]

Transient ischaemic attacks

TIAs are neurological deficits of ischaemic origin that typically last from a few minutes to usually no more than 30 min.[18] A TIA may be indistinguishable from an ischaemic stroke at presentation, and patients need to be managed as per acute ischaemic stroke guidelines if presenting within 24 h of onset with persistent weakness. TIA is pathophysiologically identical to ischaemic stroke, but the symptoms are transient because reperfusion occurs, either from adequate collateral circulation or some degree of reperfusion.

A focused history is essential, as TIA mimics, such as migraine aura or focal epilepsy, are commonly mistakenly diagnosed as TIA and subsequently inappropriately managed. In cases of diagnostic uncertainty, MRI with diffusion-weighted imaging (DWI) and blood-sensitive sequences are recommended. All patients with suspected TIA or minor stroke should be assessed urgently by a stroke specialist. Diffusion-weighted MRI should be used as it can aid in confirming or refuting the diagnosis (i.e. detecting mimics), and, if positive, in classifying the arterial territory and mechanism of the TIA, except where contraindicated, in which case CT is undertaken. Recent evidence suggests that blood-sensitive MRI sequences should also be performed to exclude TIA syndromes related to intracranial bleeding.

The ABCD2 score (see Table 4.2) has been used to risk stratify TIA to predict stroke risk. However, it is falling out of favour due to evidence

Table 4.2 ABCD2 score

Age ≥60	1 point
BP ≥140/90	1 point
Clinical features:	2 points
Unilateral weakness	1 point
Speech disturbance without weakness	
Duration of symptoms:	2 points
≥1h	1 point
10–59 min	
Diabetes	1 point

Reproduced from Lancet, 369(9558), Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S, Validation and refinement of scores to predict very early stroke risk after the transient ischaemic attack, pp. 283–92, Copyright (2007), with permission from Elsevier.[19]

supporting the scores inability to do this convincingly. It is still often used to determine immediate antiplatelet treatment.

The risk of stroke within 48 h of TIA based on ABCD2 score is:

1% in low-risk patients with a score of 1–3.
4.1% in moderate-risk patients with a score of 4–5.
8.1% in high-risk patients with a score of 6–7.

Treatment

Antiplatelet therapy after TIA is based upon determination of TIA risk based on ABCD2. Secondary prevention of modifiable risk factors needs to be implemented as soon as possible.

Acute management

For patients with ABCD2 ≥4 presenting within 24 h, it is reasonable to load clopidogrel 300–600 mg and give low-dose aspirin (ASA) followed by DAPT for 3 weeks. If symptomatic large artery atheromatous disease is noted, regardless of ABCD2 score treatment with DAPT should be 90 days. After this time period, antiplatelet monotherapy is preferred.

For patients who are dissimilar from those enrolled in CHANCE or POINT, antiplatelet monotherapy is preferred, with low-dose ASA generally considered first line. For patients with TIA and atrial fibrillation immediate treatment with a direct oral anticoagulant (DOAC) is recommended.

Evidence base

There is high-quality evidence for the use of antiplatelet therapy early after acute ischemic stroke (AIS) or TIA.[20]. There is also high-quality evidence for the use of DAPT in high-risk TIA and AIS. The International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) established the use of aspirin (160 mg 300 mg) within 48 h of TIA and AIS avoiding death and disability for almost 10 per 1000 patients treated.[21] The Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE—clopidogrel 300 mg loading dose, then 75 mg daily for 90 days and aspirin 75 mg for 21 days) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic

Stroke (POINT—clopidogrel 600 mg loading dose, then 75 mg for 90 days and aspirin 50–325 mg for 90 days) trials established the efficacy of DAPT in high-risk TIA and AIS. Several systematic reviews and meta-analyses (which include patients from these studies) further support the use of DAPT.[22,23] Notably due to exclusion criteria in these studies, the results are not generalizable to all patients. Both studies excluded isolated sensory symptoms, isolated visual symptoms, and isolated dizziness or vertigo.

Secondary prevention following ischaemic stroke or transient ischaemic attack

- Patients diagnosed with stroke and TIA have a high risk of recurrent ischaemic events. In fact, ~25% of all strokes are recurrent events, and the risk of stroke in a patient who has had a TIA is about 10% per year. In addition, these patients have a higher risk of cardiovascular, renovascular, and peripheral vascular disease. Thus, appropriate secondary prevention is crucial. Ongoing treatment with antiplatelets is recommended, and additional factors must be considered and appropriately monitored as follows.

Antiplatelet therapy

- Longer-term secondary prevention:
- aspirin 75 mg (UK) 81 mg (USA) od or clopidogrel 75 mg od.

Vascular risk factors

1. *Lifestyle*: advice should be given regarding lifestyle, including smoking cessation, dietary advice, weight control, avoidance of excess alcohol, and optimization of physical activity.
2. *BP*: a definitive target BP after the acute phase of stroke has not been established, although normotension within a physiological range is generally regarded appropriate. An average longer-term reduction of 10/5 mmHg is associated with improved outcomes in clinical trials. The most effective antihypertensive agent to prevent stroke is not known. However, benefit has been demonstrated for angiotensin-converting enzyme (ACE) inhibitors, thiazide-like diuretics, and calcium channel blockers. Recent data emphasize the importance of consistent optimized BP control to reduce variability, particularly to prevent ICH; there is some evidence that calcium channel blockers may reduce BP variability more than other agents.[24]
3. *Lipid levels*: in both the UK and USA, statin therapy is recommended for any patient who has had a stroke or TIA, unless any contraindications to their use exist (see Statins, p. 454). In the UK, guidelines recommend that statins should be started 48 h after the onset of symptoms but should not be stopped in those who are already on treatment for ischaemic stroke, while, in the USA, statins may be started following symptom onset.

Evidence base

- A meta-analysis of >90 000 patients taking part in previous statin trials demonstrated that the larger the reduction in low-density lipoprotein (LDL) cholesterol, the lower the risk of consequent ischaemic stroke.[25] The efficacy of statin therapy in the secondary prevention of ischaemic stroke is well documented. It has also been demonstrated that statin therapy should be initiated as swiftly as possible following ischaemic stroke (see Statins, p. 454). The *HPS* study involved 3280 adults with cerebrovascular disease who had previous non-disabling ischaemic stroke, TIA, and/or a history of carotid endarterectomy or angioplasty. Patients were allocated to either 40 mg simvastatin or placebo and monitored over a 5-year treatment period. Retrospective subset analysis of these patients with symptomatic ischaemic cerebrovascular disease demonstrated a 20% reduction in major vascular events (HR 0.80, 95% CI 0.71–0.92) and a 19% (non-significant) reduction in further ischaemic stroke.[26] Similarly, on-treatment analysis of 4162 patients involved in the *SPARCL* trial revealed an 18% reduction of further ischaemic stroke in those treated with 80 mg atorvastatin daily, when compared to placebo (HR 0.82, 95% CI 0.69–0.98; $p = 0.03$).[27]

4. *Diabetic control*: strict glycaemic control in diabetics reduces microvascular, and macrovascular, complications. The goal for HbA1c should be ≤7% (IFCC 53.0). In the IRIS study, patients with recent ischaemic stroke or TIA without diabetes but who had insulin resistance alone had a lower risk of recurrent stroke or MI if they received pioglitazone compared to those who received placebo.[28]

Atrial fibrillation

AF is the most common cause of cardioembolic stroke. Any patient with AF who has had a stroke or TIA, in the absence of any clear contraindications, qualifies for oral anticoagulation, according to his or her CHADS2 and CHADS2 VASc score.[29,30] These are the most used risk stratification scores used to assess the risk of cardioembolic stroke in patients with AF.

The most used anticoagulant is warfarin, but the direct oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban have emerged as attractive alternatives to warfarin for stroke prevention in AF. They have shown similar efficacy for stroke prevention and generally lower rates of ICH, compared to warfarin, in randomized controlled trials. Another benefit is the lack of requirement for regular monitoring and dose adjustment.[31–34]

Anticoagulation for long-term secondary prevention in patients with AF can be safely commenced 2 weeks post-ischaemic stroke or TIA, as demonstrated in the European Atrial Fibrillation Trial.[35] Some clinicians begin anticoagulation earlier, considering the extent of cerebral infarction, e.g. starting immediately after TIA or after a few days for small infarcts. Randomized trials are needed and are ongoing (e.g. OPtimal TIMing of Anticoagulation After Acute Ischaemic Stroke: OPTIMAS) to clarify the optimum timing of anticoagulation in acute ischaemic stroke. The commonest time point for haemorrhagic transformation post-ischaemic stroke is in the first 1–4 days after symptom onset, but later haemorrhage from

7–14 days (and occasionally beyond) can occur. Cerebral microbleeds are associated with an increased hazard of intracranial haemorrhage in patients anticoagulated after cardioembolic stroke due to AF; this has been investigated in the CROMIS-2 observational study where symptomatic intracranial haemorrhage rate in patients with cerebral microbleeds was 9.8 per 1000 patient-years (95% CI 4.0–20.3) compared with 2.6 per 1000 patient-years (95% CI 1.1–5.4) in those without cerebral microbleeds (adjusted hazard ratio 3.67, 95% CI 1.27–10.60).[36] The Microbleeds International Collaborative Network (MICON) recently determined, in a study of 7839 patients, that combination anticoagulant and antiplatelet therapy for the treatment of AF in the presence of microbleeds resulted in an increased relative risk of ICH, which correlated with microbleed burden (2–4 microbleeds (AR 25 vs. 12 per 1000 patient-years)) and ≥11 microbleeds (AR 94 vs. 48 per 1000 patient-years). The study concluded that patients with a high burden of microbleeds receiving dual therapy for atrial fibrillation were at higher risk of I CH than AIS and hence were at risk of net harm using this approach.[37]

Paradoxical embolism

While previously controversial, recent randomized controlled trials support the consideration of patent foramen ovale (PFO) closure for certain patients presenting with stroke unlikely related to other aetiologies.[38] The risk of paradoxical embolism (ROPE) score can be helpful to determine candidacy for this procedure.[39] Points are accrued for not having hypertension, diabetes, or smoking history, cortical infarct location, and young age. The higher the score, the more likely the stroke is related to PFO.

Extracranial carotid or vertebral artery dissection

In the setting of extracranial vertebral or carotid artery dissection causing ischaemic stroke, antiplatelets, or oral anticoagulation are considered in the acute setting; however, evidence has failed to consistently demonstrate any benefit of anticoagulation over antiplatelet therapy.[40,41] Patients with high subsequent risk of thrombosis, severe stenosis, or occlusive dissection may benefit with anticoagulation acutely.[42] Antiplatelets are usually started after 24 h. Anticoagulation is usually started 24 h after thrombolysis and depending on stroke burden, haemorrhagic transformation risk, and physician experience. Direct oral anticoagulants (DOAC) can be started 48 h after stroke due to their rapid onset of action.[42] Cochrane analysis of over 30 observational studies suggested there was no significant difference in the odds of ischaemic stroke or death between the two treatments, although there may be a non-significant trend towards reduced death or disability in favour of oral anticoagulants (OR 1.77; p = 0.06). More intra- and extracranial haemorrhages occurred in the anticoagulated group.[43] The CADISS trial found no difference in the efficacy of antiplatelet and anticoagulant drugs in preventing stroke and death in patients with symptomatic carotid and vertebral artery dissection; however, many patients were not enrolled until several days after their stroke presentation and there were few outcome event.[44] The TREAT-CAD trial did not find aspirin to be non-inferior to vitamin K antagonists in the treatment of cervical artery dissection.[45] Currently, many stroke physicians consider anticoagulation or dual antiplatelet treatment in the acute setting for 3–6 months with interval imaging to visualize the symptomatic vessels to assess for resolution and then switch to antiplatelets unless otherwise indicated. If started in the acute setting antiplatelets are continued lifelong as secondary prevention for stroke. Vitamin K antagonists were the agents of choice in the majority of studies. Limited data is available for DOACs in this setting. Anticoagulation should be avoided in the much rarer setting of intracranial arterial dissection due to the risk of catastrophic SAH.

Symptomatic carotid artery stenosis

Symptomatic carotid artery stenosis represents a subgroup of ischaemic strokes whereby atherosclerosis is present within the supplying carotid artery.

It is important to clinically separate this group of patients, as they may benefit from carotid revascularization procedures, i.e. carotid endarterectomy (CEA) or stenting procedures. These techniques aim to prevent further thromboembolic strokes arising from symptomatic carotid arteries. Endarterectomy is more commonly used and current practice is to consider all patients with symptomatic carotid stenosis >50% for revascularization, following multidisciplinary team discussion. Specific plaque characteristics, e.g. ulceration (on non-invasive angiography) or intraplaque haemorrhage (on dedicated MRI) may help to predict high early stroke risk in carotid stenosis.

For patients with ischaemic stroke or TIA due to symptomatic intracranial stenosis, DAPT (aspirin and clopidogrel) may be considered following the SAMMPRIS trial, which showed the superiority of aggressive of medical treatment compared with endovascular treatment (stenting).[46] Short-term DAPT (e.g. 3–4 weeks) is also often recommended for patients with symptomatic extracranial arterial stenosis (e.g. carotid or vertebrobasilar stenosis).

Intracerebral haemorrhage

ICH is associated with a significant risk of further ICH of about 5–10% per year. The risk is much higher for ICH due to CAA than for ICH related to arteriolosclerosis (hypertensive arteriopathy).

The focus of pharmacological treatment of ICH is prevention of haematoma expansion. Thus, any coagulopathy needs to be normalized, and extremes of BP should be controlled as quickly as possible:

1. Haemostatic agents: in patients taking anticoagulants, rapid administration of a reversal agent is required. In the context of warfarin, this is usually IV vitamin K, with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), depending on

local availability. The intracranial haemorrhage related to vitamin K antagonists (INCH) trial found that PCC is superior to FFP in normalizing the INR and lessening haematoma expansion in vitamin K antagonist-related ICH but was not powered to demonstrate improved outcomes.[47] Protamine sulphate should be given to reverse heparin. The novel oral anticoagulants apixaban and rivaroxaban may be reversed with andexanet alfa, whilst dabigatran can be reversed with idarucizumab (Praxbind).[48,49] There is no currently approved reversal agent for edoxaban. Platelet transfusion has been shown to be unhelpful (and likely harmful) in acute ICH in patients taking antiplatelets (PATCH trial).[50] They have been shown to have utility in patients with ICH prior to neurosurgical evacuation.[51]

2. Antihypertensives: Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial using IV nicardipine and the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT-1 and 2) using a mixture of antihypertensives have both demonstrated that systolic BP reduction to 140mmHg is well tolerated and associated with attenuation of haematoma expansion. The ATACH-2 trial suggested that more intensive treatment in acute ICH to achieve a target systolic blood pressure of 110 to 139 mmHg did not result in a lower rate of death or disability than reduction to a target of 140 to 179 mmHg. Thus, rapid BP lowering beyond a target of 140 mmHg systolic is not recommended in acute ICH.[52–55]

Management of blood pressure in intracerebral haemorrhage

1. the effects of anticoagulant agents should be urgently reversed, and any other coagulopathy corrected, if possible.
2. There is uncertainty with regards to optimal systolic BP control after stroke due to intracerebral haemorrhage. An ordinal shift analysis of INTERACT-2 found improved functional outcomes with intensive lowering of blood pressure to below 140 mmHg systolic (compared to standard care) within 6 h in patients with initial blood pressure 150–220 mmHg.[54] ATACH-II found no difference in mortality or morbidity with intensive BP control (110–139 mmHg) compared to standard control (140–179 mmHg).[55] One strategy is aiming for a target of <140 mmHg systolic for the first 24 h and then liberalize to <160 mmHg, unless there is a clear contraindication. In the UK, NICE guidance advises considering treatment (if no contraindication—see next) if presentation is within 6 h of symptom onset with a systolic BP between 150 and 220 mmHg or if presenting beyond 6 h of symptom onset with systolic BP >220 mmHg; target 130– 140 mmHg within 1 h of starting treatment and maintain this for 7 days.[56]

Contraindications:

1. underlying structural cause (e.g. AVM, tumour etc.)
2. GCS <6
3. early neurosurgery for hematoma evacuation or
4. massive hematoma with poor prognosis)

As intensive BP management in ATACH-II was associated with an increased incidence of renal failure, a suggested target of 130 mmHg was set by NICE.

All patients should be admitted to a dedicated stroke unit (or neuro-intensive care with access to neurosurgery if intensive treatment, monitoring, or neurosurgical intervention is required).

Surgical interventions

Surgical decompression of large intracranial haemorrhages may be indicated for patients with symptomatic hydrocephalus, significant neurological disability, and/or evidence of elevated ICP. Non-invasive surgical approaches in ICH show promise. Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation (MISTIE) 3 found at 1-year post-ICH, functional recovery was not improved when comparing the image-guided minimally invasive MISTIE procedure to traditional medical therapy to treat medium to large volume intracerebral haemorrhage. It may reduce death, and more benefit was seen with a smaller residual volume.[57] The procedure involved creation of a burr hole and insertion of a rigid catheter into the clot followed by syringe aspiration of the clot until first resistance, followed by replacement with a soft catheter. Subsequent alteplase instillation via the catheter (1.0 mg in 1 mL followed by 3 mL flush every 8 h, for up to nine doses).[57] MISTIE III found that the greater the reduction in volume of the ICH during surgery, the greater the likelihood of a good functional outcome, with ≤15 mL indicated as a threshold.

Secondary prevention of intracerebral haemorrhage

The main target for secondary prevention is reduction of BP; the PROGRESS trial showed that the benefit of BP reduction after ICH exceeded the benefit seen in ischaemic stroke.[58] The optimum target is unknown, but a target of less than 140 mmHg is usually recommended; observational data suggest that sustained BP control (smoothing out high peaks) may be especially important in preventing ICH. Other modifiable risk factors linked to ICH recurrence include diabetes, excessive alcohol consumption, and cigarette smoking.

Anticoagulants, antiplatelets, and statins following intracerebral haemorrhage

Unless there is a clear indication, antithrombotics (antiplatelets and anticoagulants) should be avoided after ICH, particularly in the presence of CAA. There is inconclusive data on statin use and recurrent ICH risk. In CAA where some experts recommend avoidance in the absence of a clear indication, with a preference for hydrophilic agents (e.g. pravastatin and rosuvastatin).[59] The RESTART trial found only a marginal reduction in the risk of recurrent ICH in patients given antiplatelet therapy who were on antithrombotic therapy for the prevention of occlusive vascular disease when they developed ICH. These results suggest that subsequent antiplatelet therapy did not increase the risk of further ICH for up to 5 years.[60]

Evidence base

When haemorrhagic stroke has occurred in association with oral anticoagulant or antiplatelet agent use, a risk–benefit analysis needs to be undertaken, weighing up the possible chances of a re-bleed with the chance of a recurrent thrombotic event. There is no clear evidence in this area. Several ongoing trials are investigating when to restart an oral anticoagulant or antiplatelet agents following an intracranial bleed and will hopefully inform management in this challenging area. The APACHE-AF trial found no difference in the risk of non-fatal stroke or vascular death between groups on anticoagulation (apixaban) or no anticoagulation in patients with AF that suffered an initial ICH while on anticoagulation.[61] The SO-START trial did not establish non-inferiority of oral anticoagulation against avoiding anticoagulation between groups that suffered ICH while on anticoagulation for AF.[62] PRESTIGE-AF (NCT03996772), A3ICH (NCT03243175) and ENRICH-AF (NCT03950076) will provide further insights into the appropriate management of AF following ICH.

In patients with ICH with a high risk of future ischaemic stroke due to AF, but who are judged to have an unacceptably high ICH risk to safely allow long-term oral anticoagulation, left atrial appendage occlusion, which appears to be as safe and effective as oral anticoagulation with warfarin, may be reasonably considered.[63]

The use of statins after ICH remains controversial. In the SPARCL trial, patients with ICH at baseline had a higher risk of future ICH when treated with atorvastatin, compared with placebo.[64] Moreover, some studies have found an inverse relationship between total and LDL-cholesterol and the risk of ICH. However, subsequent studies and meta-analyses have not confirmed definitively whether statins increase the risk of future ICH and show a clear benefit on overall mortality and functional outcome. It is therefore reasonable to balance the benefits and possible risks of statin therapy in individual patients, according to an assessment of the risks of vaso-occlusive events and future recurrent ICH.[59]

Subarachnoid haemorrhage

- SAH accounts for ~5% of strokes and has an incidence rate of 6–9 per 100 000 patient-years. It typically occurs in patients <60 years of age. The commonest causes of SAH are aneurysmal rupture (particularly saccular berry aneurysms, 85%), arteriovenous malformations, trauma, clotting disorders/anticoagulants, tumours, and vasculitis. It classically presents with a sudden and severe ('thunderclap') headache, worst at the occiput and associated with neck stiffness, presumably secondary to blood in the subarachnoid space. Dizziness, nausea, and vomiting (which may be transient or protracted) can also be experienced. Impaired level of consciousness and focal neurological signs may occur, particularly if there is associated ICH. Seizures occur in ~7% of patients.
- In patients with a typical history, an urgent high-resolution non-contrast CT head scan within 12 h of symptom onset has a sensitivity of 98–100%.[65] Sensitivity falls to 93% at 24 h, further declining to 57–85% at 6 days.[66] If there is a highly suggestive history and no evidence of

haemorrhage on an acute CT scan, then an LP is recommended to confirm or refute a diagnosis of SAH by looking for the presence of xanthochromia at ~12 h after symptom onset. This is present in 100% of patients up to 14 days, and in 70% up to 21 days, after SAH onset.[67] MRI fluid-attenuated inversion recovery (FLAIR) and susceptibility-weighted (SWI) sequences may be helpful in patients with normal CT scans and equivocal cerebrospinal fluid (CSF) results, although routine use in the acute scenario is often difficult due to lack of availability.[68]

Management

The acute management of SAH involves resuscitation and early implementation of interventions designed to prevent common complications, namely further bleeds, vasospasm, and hydrocephalus.[66,69] The following measures must be taken to stabilize the patient.

1. *Resuscitation and neuro-observations*: advanced life support techniques, particularly fluid resuscitation, to maintain cerebral perfusion, and close neurological monitoring are important.
2. *BP control*: systolic BP should be maintained between 90 and 140 mmHg prior to aneurysm treatment. Hypotension should be corrected to maintain adequate cerebral perfusion and prevent vasospasm. Hypertension should be corrected with antihypertensives that can be titrated rapidly. If there are no contraindications, IV labetalol is the agent of choice.
3. *Prevention of vasospasm*: patients should be adequately hydrated, electrolyte abnormalities corrected, and nimodipine 60 mg 4-hourly (or as close to this as tolerated) initiated. Nimodipine, at this dose, has been demonstrated to reduce the chance of cerebral infarction, following SAH, from 33% to 22%. This correlates with improved clinical outcomes.
4. *Management of raised ICP* (see Raised intracranial pressure, p. 230 in Chapter 16, Neuro-oncology): patients with signs of raised ICP or brain herniation may require intubation, consideration of hyperosmolar therapy, and hyperventilation. The use of excessive hyperventilation, as well as agents, such as mannitol, which may cause dehydration and hypotension, should be avoided in order to prevent worsening vasospasm.
5. *Seizure prophylaxis*: this is currently an area of significant uncertainty. Some studies have demonstrated no connection between functional outcome and seizures, and retrospective investigations have demonstrated adverse effects from anti-seizure medicines (ASMs). Nonetheless, seizures may potentially increase the risk of re-rupture of an unsecured lesion. Long-term prophylactic anticonvulsant therapy is not routinely recommended.
6. *Analgesia and antiemetics*: these are important to minimize distress and ensure adequate hydration and the maintenance of a steady BP.
7. *Definitive neuroradiological or neurosurgical treatment*: following confirmation of the diagnosis and appropriate stabilization of the patient, early discussion with a regional neurosurgical centre is essential to identify scope for neuroradiological or neurosurgical intervention.

Cerebral venous sinus thrombosis

Thrombosis in the cerebral veins is an uncommon and under-recognized form of stroke. It accounts for 0.5–1% of all strokes and occurs more commonly in young individuals. Risk factors include dehydration, ear or sinus infections, long-haul air travel, trauma, surgery, oral contraceptives, inflammatory bowel disease, pregnancy, and prothrombotic haematological conditions.

Headache is common and usually diffuse in nature, progressing in severity over days to weeks, although occasionally there is a thunderclap presentation, causing diagnostic confusion with SAH. Focal neurological deficits are usually due to focal brain injury from infarction or haemorrhage. Appropriate investigations include CT venography (to detect sinus filling defects), T2*-weighted MRI (to visualize the thrombus directly and detect areas of haemorrhage or infarction), and magnetic resonance (MR) venography. Digital subtraction angiography can help to clarify cases of diagnostic uncertainty, despite non-invasive testing.

Treatment

In the acute setting, anticoagulation, typically intravenous heparin or subcutaneous low molecular weight heparin (LMWH) should be started, even if there is haemorrhage on brain imaging (unless surgical intervention is imminent). Anticoagulation has been shown to be safe and effective in small, randomized trials.[70] There is no evidence to support the use of antiplatelet agents in cerebral venous sinus thrombosis.

In those patients who deteriorate despite anticoagulant therapy, endovascular thrombolysis (e.g. with direct administration of recombinant tissue plasminogen activator (rt-PA) into the occluded sinus through an IV catheter) or mechanical disruption/removal of the thrombus have been tried, but with no clear evidence of benefit.[1,71] Long-term management is with oral anticoagulants. Treatment duration is typically 3–12 months, depending on the presence and nature of risk factors for venous thromboembolism (VTE). In cases with an underlying thrombophilia tendency or recurrent cerebral venous thrombosis, treatment may be recommended lifelong. Vitamin K antagonists are most widely used, although recent data has supported the equal efficacy of DOACs. Due to their relative ease of use may be preferred.[72]

Vaccine-induced immune thrombotic thrombocytopenia associated cerebral venous thrombosis (VITT-CVT)

VITT-CVT is a novel and rare entity described 5–30 days post-vaccination for SARS-CoV-2.[73] The mechanism of the disorder is like autoimmune heparin-induced thrombocytopenia (HIT) with antibody formation against the PF4 platelet antigen.

As such, treatment involves the use of

(1) immunomodulation (IVIG, PLEX, Eculizumab)
(2) non-heparin anticoagulants (direct thrombin inhibitors, anti-Xa agents and fondaparinux) are preferred but heparin appears to be safe. Vitamin K antagonists should be avoided due to the induced protein C deficiency.
(3) avoidance of platelet transfusion where feasible due to possibility for immune-mediated worsening.

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Chapter 5

Neuropathic pain

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Introduction

Neuropathic pain can be defined as '*pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system*'.[1] This is distinct from nociceptive pain, which is '*pain resulting from a noxious stimulus*'.[1] Neuropathic pain syndromes comprise a heterogeneous group of disorders. Various studies have estimated that between 1% and 8% of Western populations may be affected. When considering specific diseases, roughly 30–50% of people with diabetes will suffer from neuropathic pain,[2] and 10–20% of patients will develop post-herpetic neuralgia following shingles.[3]

Classification

The following classification system is based on the clinical grouping of conditions that is used in most neuropathic pain trials and in the European Federation of the Neurological Societies (EFNS) guidelines on the management of neuropathic pain:

- painful neuropathies (mono-/polyneuropathies):
  - polyneuropathies—hereditary, toxin-/drug-related, immune-mediated, metabolic.
  - diabetic mononeuropathy, polyneuropathy, amyotrophy.
  - post-herpetic neuralgia.
  - infective/post-infective, e.g. HIV neuropathy.
  - carcinoma-related, e.g. paraneoplastic, myeloma.
  - phantom pain.
  - nerve trauma.
- chronic radiculopathy.
- central pain syndrome.
- trigeminal neuralgia.
- complex regional pain syndromes, e.g. fibromyalgia.

Treatment of neuropathic pain

Initiation: when starting pharmacotherapy for neuropathic pain, consideration should be given to the aetiology and severity of the pain, including its impact on activities of daily living and sleep, as well as patient factors such as co-morbidities and age.

Review: patients should be reviewed soon after initiation of treatment and regularly thereafter to assess efficacy and tolerability and to monitor dose titration. A specialist pain service may be useful if pain is severe, there is poor response to initial management, or if psychological factors are prominent.

Withdrawal: medication cessation should be undertaken gradually and the patient closely monitored for any aggravation of pain or withdrawal symptoms.

The following recommendations from the Special Interest Group on Neuropathic Pain (NeuPSIG) are based on a meta-analysis of efficacy which included 229 studies.[4]

First line:	Gabapentinoids	Gabapentin 150–600 mg/day
		Pregabalin 300–3600 mg/day
	TCAs	Amitriptyline 10–150 mg/day
	SNRIs	Duloxetine 20–120 mg/day
		Venlafaxine 150–225 mg/day
Second line: Opioids		Tramadol 25–400 mg/day
		Tapentadol 50–600 mg/day
	Topical treatment	Lidocaine 5% patches or gel
	Capsaicin 8% patches	
Third line:	Strong opioids	Morphine 10–120 mg/day
		Oxycodone 10–120 mg/day
	Neurotoxin	Botulinum toxin 25–300 U

Treatment of individual neuropathic pain syndromes

These evidence-based recommendations are from the 2010 EFNS guidelines for the treatment of neuropathic pain.

Painful polyneuropathy

This is an aetiologically diverse group of conditions, excluding post-herpetic neuralgia, diabetic neuropathy, and HIV neuropathy. Painful polyneuropathy can be caused by drugs, toxins, gammopathies, and inflammatory, paraneoplastic, and metabolic conditions. Painful neuropathy may also be a feature of a number of inherited diseases, including hereditary sensory and autonomic neuropathies, familial amyloid polyneuropathies, and mitochondrial disorders.

Treatment

- *First line*: gabapentin, pregabalin, or TCAs.
- *Second line*: tramadol.
- *Third line*: strong opioids.

Evidence base

A meta-analysis of several small RCTs demonstrated the efficacy of TCAs (NNT 2.1, 95% CI 1.8–2.6) in painful polyneuropathy.[5] Despite good evidence of efficacy of duloxetine, gabapentin, and pregabalin in diabetic painful polyneuropathy, there are no substantial trial data for their use in painful polyneuropathy of other aetiologies.

Diabetic neuropathy

This is the most prevalent sensory neuropathy in Europe and the USA, usually presenting as a chronic distal sensory small-fibre, or mixed small- and large-fibre polyneuropathy. Good glycaemic control is an important preventative measure and may halt progression of the condition.

Treatment

- *First line*: SNRIs (duloxetine, venlafaxine).
- *Second line*: gabapentin, pregabalin, or TCAs.
- *Third line*: Opioids (tapentadol).

Evidence base

A number of robust RCTs demonstrate efficacy of duloxetine for pain relief in diabetic neuropathy. These data have been consolidated in a meta-analysis demonstrating an NNT of 5 (95% CI 4–7) for a 50% reduction in pain over 12 weeks.[6] Gabapentin, TCAs, and pregabalin have all been shown to be effective in meta-analyses with an NNT for 50% pain reduction of 5.8 (95% CI 4.3–9), 1.3 (95% CI 1.2–1.5), and 5.0 (4.0–6.6), respectively.[7] Tapentadol is the only opioid currently FDA-approved for the management of painful diabetic neuropathy.[8]

Post-herpetic neuralgia

Post-herpetic neuralgia is a common form of neuropathic pain that can follow shingles (dermatomal reactivation of varicella zoster). It is more common in the elderly and complicates shingles in ~20% of people.[3] The pain, which affects the dermatomal level(s) involved by the zoster rash, usually starts after the herpetic vesicles have crusted over, and typically lasts for over 3 months.

Treatment

- *First line*: gabapentin, pregabalin, TCAs, or topical lidocaine (in the elderly).
- *Second line*: strong opioids or topical capsaicin.

Evidence base

There is good evidence from multiple large RCTs and meta-analyses for the efficacy of gabapentin, pregabalin, and TCAs in the treatment of post-herpetic neuralgia. The NNT for 50% pain reduction was 7.5 (95% CI 5.2–14) for gabapentin 1800 mg daily,[7] 4.0 (95% CI 3.1–5.5) for pregabalin 600 mg daily,[9] and 2.2 (95% CI 1.6–3.1) for global improvement in pain scores with TCAs.[5]

Two RCTs have confirmed that strong opioids are effective (1.9-fold reduction in pain intensity; $p < 0.001$).[10] There are data from two placebo-controlled RCTs demonstrating marginal efficacy for lidocaine patches in post-herpetic neuralgia; however, they are expensive, and thus European Federation of the Neurological Societies (EFNS) and National Institute for Health and Care Excellence (NICE) recommend their use only for patients who cannot tolerate/use oral medications, particularly the elderly.[11,12]

Finally, there is strong evidence from a meta-analysis for the efficacy of high-strength (8%), but not low-strength, topical capsaicin (NNT = 8.8, 95% CI 5.3–26).[13]

HIV neuropathy

HIV commonly causes a painful distal symmetric axonal polyneuropathy. The neuropathological mechanism is unknown.[14] Importantly, dideoxynucleoside reverse transcriptase inhibitor drugs used extensively in HIV treatment can also cause an acute toxic neuropathy.[14]

Treatment

- *First line*: topical capsaicin or lamotrigine.
- *Second line*: cannabinoids.

Evidence base

Most conventional pharmacological treatments for neuropathic pain do not effectively alleviate symptoms associated with HIV neuropathy. Moderate evidence for efficacy has been demonstrated from small individual placebo-controlled RCTs for lamotrigine (57% received pain relief vs. 23% with placebo; $p = 0.004$),[15] smoked cannabis (34% received pain relief vs. 17% with placebo; $p = 0.03$),[16] and the high-dose capsaicin patch (22.8% received pain relief vs. 10.7% with placebo; $p = 0.0026$).[17]

Cancer-related neuropathic pain

Cancer-related neuropathic pain can be due to remote or local effects of the disease, or secondary to chemotherapy. Cancer pain is usually of mixed aetiology, rather than purely neuropathic, and so strong opioids are often used. In addition to conventional therapies for neuropathic pain, there may also be opportunities to target pain through oncological therapies.

Treatment

- *First line*: gabapentin.
- *Second line*: TCAs or tramadol.

Evidence base

There are few good-quality clinical trials of treatment of neuropathic pain associated with cancer. There is some evidence showing efficacy for gabapentin (0.8 point reduction in pain intensity, compared to placebo; $p = 0.025$),[18] and tramadol (improvement in pain scores; $p < 0.001$) in one RCT.[19] The only RCT of TCAs in cancer-associated neuropathic pain found no benefit from adding amitriptyline to morphine.

Phantom pain

Phantom pain is due to aberrant cortical sensory perception of an amputated body part. Its reported incidence varies widely between studies because of differing definitions of phantom pain. At least 80% of amputees will experience abnormal sensations in the amputated body part at some point. When phantom pain does manifest, it occurs within days of the operation/injury in 75% of cases.

Evidence base

There are conflicting recommendations for the treatment of phantom pain. The oral analgesic with the best efficacy in trials is morphine (53% pain relief, compared to 19% with placebo; $p < 0.0001$; NNT for 50% pain relief = 5.6).[20] Gabapentin has shown discrepant results in RCTs. There is evidence for the preoperative use of IV morphine and IV ketamine and for the use of perioperative epidural anaesthesia with morphine and bupivacaine.[12]

Traumatic neuropathic pain

Nerve damage can occur following trauma and surgery, approximately 3% of trauma victims sustaining significant peripheral nerve injury and a large proportion of these suffering from long-term neuropathic pain. Trauma may also be iatrogenic, particularly in oral and maxillofacial surgery. An estimated 0.5–2% of maxillofacial procedures will result in the development of long-term neuropathic pain.

Treatment

- *First line*: amitriptyline.
- *Second line*: botulinum toxin and gabapentin.

Evidence base

There is minimal evidence for pharmacotherapy in traumatic neuropathic pain.[12] Gabapentin achieved only a few secondary outcome measures in a multicentre trial.[21] In individual smaller trials, amitriptyline reduced pain by 50% in 8/15 patients, and botulinum toxin injections improved global pain relief in 40%, compared to 14% with placebo ($p < 0.05$; NNT for 50% pain relief = 3.03).[12,22] However, botulinum toxin injections are not universally recognized as a treatment for neuropathic pain and are not currently licensed for this indication.

Chronic radiculopathy and plexopathy

Damage to a nerve root or roots can result in pain, as well as weakness and numbness in the root territory. Lumbar and brachial plexopathies can also cause pain. Causes include trauma, mechanical impingement, diabetes, and infections such as HIV and Lyme disease.

Evidence base

No agent has demonstrated consistent pain relief in RCTs. TCAs and strong opioids show the best results.

Central neuropathic pain

Central neuropathic pain is due to disruption of the pain pathways within the central nervous system (CNS). The commonest causes are stroke, MS, and spinal cord injury (SCI).

Treatment

- *First line*: amitriptyline, gabapentin, pregabalin, SNRIs.
- *Second line*: tramadol.
- *Third line*: strong opioids.

NB. Cannabinoids may alleviate central pain in patients with MS.

Evidence base

Several systematic reviews suggest a moderate effect of both pregabalin 600 mg (NNT = 5.6, 95% CI 3.5–14 for 50% pain reduction) and gabapentin (improvement in pain scores ranging from 0.873 to 3.362 on a 10-point scale; $p < 0.05$, in four RCTs) for pain following SCI.[23,24] There is weak evidence from an RCT for amitriptyline post-SCI (reduction of pain scores by 2.46 on a 10-point scale, compared to diphenhydramine; $p = 0.035$), but not post-stroke.[25] Individual RCTs provide some evidence for efficacy of strong opioids (15% pain reduction with high-dose, compared to low-dose, μ-opioid agonist; $p = 0.02$)[26] and tramadol (7/23 patients rated improvement in pain, compared to 1/12 with placebo; $p = 0.04$).[27] One RCT indicated that Sativex®, an oromucosal cannabinoid spray, may help to relieve neuropathic pain in MS (reduction in pain score by 0.79 on a 10-point scale, compared to placebo; $p = 0.038$).[28]

Trigeminal neuralgia

Trigeminal neuralgia presents with brief, intense periods of electric shock-like pain distributed along the territory of the trigeminal nerve. Classical trigeminal neuralgia is idiopathic or secondary to vascular compression of the trigeminal nerve at the cerebellopontine angle, and symptomatic trigeminal neuralgia also occurs as a result of structural lesions such as cerebellopontine angle masses or MS.

Treatment

- *First line*: carbamazepine or oxcarbazepine.
- *Second line*: lamotrigine or phenytoin.

Evidence base

Carbamazepine has been used to treat trigeminal neuralgia since the 1960s. As such, much of the evidence is anecdotal or from very old and small trials. A recent meta-analysis combined two trials of 98 patients and demonstrated that carbamazepine provided better analgesia than placebo, with an NNT of 2 (95% CI 1–2).[12,29] Three RCTs support the use of oxcarbazepine in place of carbamazepine on the basis of comparable efficacy (88% of patients achieve a reduction in attacks by >50%) and a superior side effect profile.[29,30] A recent Cochrane review concluded that there is insufficient evidence to recommend lamotrigine for trigeminal neuralgia, despite one RCT demonstrating a beneficial effect.[31,32] Finally, microvascular surgical decompression may be of benefit for drug-resistant classical trigeminal neuralgia.

Combination pharmacotherapy in neuropathic pain

A systematic review and meta-analysis assessed currently available data for combination therapy in neuropathic pain and concluded that there was insufficient evidence to advise any specific combination if monotherapy fails.[33] Both NICE guidelines and the International Association for the Study of Pain (IASP) guidelines concur.[34]

On the basis of past and current clinical practice, the following drug combinations may be beneficial (EFNS guidelines[29]):

1. TCAs in combination with pregabalin.
2. Duloxetine in combination with pregabalin.

3. Tramadol as an adjunct in any neuropathic pain syndrome.
4. Gabapentin, in combination with a TCA or a strong opioid.

Other drugs

Other antidepressants: There is very little evidence for efficacy of SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline) for neuropathic pain. Most trials have been too small and/or show conflicting results. The only meta-analysis to assess SSRIs in neuropathic pain concluded that better-quality data are required. The antidepressants phenelzine (MAOI) and bupropion (NDRI) have shown some benefits in small trials, but St John's Wort and trazodone (SARI) have appeared ineffective in studies to date. None of these drugs are currently recommended for the treatment of neuropathic pain by any international body, and they are not licensed for this indication in the UK or USA.

Other anti-seizure medications (ASMs): a meta-analysis assessed the efficacy of ASMs in neuropathic pain and fibromyalgia. Good second-tier evidence was found for gabapentin and pregabalin, but no significant evidence of efficacy was identified for clonazepam, phenytoin, and sodium valproate. Lacosamide, lamotrigine, and topiramate were deemed either ineffective or at best minimally effective.

Emerging therapies for neuropathic pain

In addition to the drugs discussed in detail in this section, several other drugs and technologies have shown benefit in phase III clinical trials of neuropathic pain but are not at the time of writing approved by U.S. Food and Drug Administration (FDA) or European Medicines Agency (EMA) for clinical use.

1. NMDA receptor antagonists
   Perioperative ketamine has shown benefit in reducing long-term neuropathic pain after thoracotomy, and memantine prevented post-mastectomy pain and diminished chemotherapy-induced pain in a single-phase III placebo-controlled trial. NMDA receptor antagonists have otherwise shown conflicting results in small trials for the treatment of phantom pain, Memantine was ineffective for pain relief in diabetic, post-herpetic, and HIV neuropathy, and dextromethorphan had no effect in post-herpetic neuralgia.
2. Cannabinoids
   Several studies support the efficacy of *Cannabis sativa* derivatives for treatment of neuropathic pain.[35] Sativex, an oro-mucosal spray containing δ9 tetrahydro-cannabinol (δ9THC) and cannabidiol (CBD) has been most investigated, and has shown benefit in MS central pain, neuropathic pain after peripheral injury and diabetic neuropathy, but not in chemotherapy-induced neuropathy.
3. Non-invasive electromagnetic stimulation techniques
   Transcranial brain stimulation with repetitive transcranial magnetic stimulation (rTMS) has shown benefit in phantom limb pain, and transcranial direct current stimulation (tDCS) has been reported as having a beneficial effect on neuropathic pain associated with diabetes,

SCI, and fibromyalgia. Repetitive spinal magnetic stimulation (SMS) can effectively relieve intractable lower limb neuropathic pain. Frequency-modulated electromagnetic stimulation (FREMS) reduces pain and enhances microvascular blood flow in diabetic neuropathy.

4. Spinal cord stimulation (SCS)/dorsal column stimulation
   This technique requires percutaneous insertion of electrodes via an epidural needle, or surgical implantation by laminectomy. Various regimens have been found to be of benefit for failed back surgery syndrome, refractory painful diabetic neuropathy, and chronic low back and leg pain.

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Chapter 6

Multiple sclerosis and related disorders

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Multiple sclerosis

Introduction

Multiple sclerosis is the most prevalent inflammatory disorder of the CNS. It affects 120 per 10 000 people in Europe and the USA, and incidence is increasing. Onset is typically in early adulthood but paediatric cases can occur and MS can present in middle age or later.

Aetiology

The cause of MS remains unknown. Both genetically determined susceptibility and an environmental trigger, possibly viral, are thought to be required. To date, over 200 MS susceptibility genes have been identified supporting a polygenic risk. Epstein–Barr virus (EBV) infection has been strongly implicated in MS pathogenesis, and vitamin D deficiency is a risk factor for the development of MS.

Clinical course

Most patients (85–90%) experience a relapsing–remitting course from onset (RRMS), with discrete episodes of neurological dysfunction (relapses) of subacute onset and lasting from days to months, with variable degrees of recovery, interspersed with periods of clinical disease inactivity (remissions). MS has a predilection for certain sites within the CNS, producing typical clinical presentations of optic neuritis, myelitis, ataxia, and brainstem syndromes. MRI appearances are characteristic with high signal lesions on T2 and FLAIR in the periventricular, subcortical, and/or juxtacortical white matter, the brainstem, cerebellum, and spinal cord.

The first presentation of MS is known as clinically isolated syndrome. A diagnosis of RRMS can be made, according to the 2017 modified McDonald Criteria,[1] as soon as there is evidence of new inflammatory activity (dissemination in time) in a different site within the CNS (dissemination in space). Dissemination in space may be met by having lesions in at least 2 of 4 locations including the periventricular region, a cortical/juxtacortical location, the brainstem, or spinal cord. The requirement for dissemination in time can be met by the occurrence of a new relapse, the co-occurrence of old and active gadolinium-enhancing lesions on the MRI scan at first presentation, new lesions on a subsequent MRI scan, or the presence of oligoclonal bands in CSF, unmatched in serum (indicating previous inflammation within the CNS).

Left untreated, most patients with RRMS eventually go on to develop secondary progressive MS (SPMS), which is characterized by a gradual accumulation of disability over years, independent of relapses. A small proportion (10–15%) of patients have gradually progressive disease from onset, termed primary progressive MS (PPMS).

Pathology

Early in the disease course, there is multifocal inflammatory demyelination occur throughout the CNS, typically involving the periventricular, cortical/juxtacortical and infratentorial white matter, the optic nerves, and the spinal cord. At this stage immunopathology is driven by auto-reactive T cells, which interact with B cells and initiate complex inflammatory mechanisms involving multiple cellular and humoral processes. Demyelination and axon loss occur due to direct immune-mediated injury from cytotoxic T cells, antibodies, and activated macrophages and microglia.

Over time and with increasing age, peripheral immune activation tends to reduce and inflammation becomes more compartmentalized (termed smouldering inflammation). Increasing disability may be driven by the expansion of existing lesions in the presence of microglial activation, cortical demyelination, meningeal B cell follicles, mitochondrial dysfunction, hypoxia, iron deposition, and secondary neurodegeneration, coupled with a failure of central compensatory mechanisms and loss of remyelination capacity.

Axon loss and compartmentalized/smouldering inflammation appears to occur throughout the course of MS, but becomes more apparent clinically over time. Axon loss and smouldering inflammation are important determinants of disability and cognitive dysfunction as the disease progresses. Brain and spinal cord volume loss, a surrogate MRI marker of axon loss, correlates closely with clinical disability in the progressive phase. SPMS and PPMS probably have a common pathology.

General principles of management of MS

The pharmacological management of MS involves treatment of relapses, disease-modifying therapy (DMT) to favourably alter the course of the disease, and symptomatic therapies to ameliorate the common symptoms of MS.

Treatment of relapses

- *First line*: PO methylprednisolone 500 mg to 1000 mg daily for 5 days or IV methylprednisolone 1 g daily for 3 to 5 days.
- Proton pump inhibitor for the duration of the steroid course.

Short courses of high-dose corticosteroids shorten relapse duration but have no impact on the degree of final recovery from a relapse or on the subsequent disease course. They are therefore reserved for functionally significant relapses. Regimes vary throughout Europe and the USA, but the authors recommend the above approach. There is no strong evidence of benefit to support the use of an oral prednisolone taper.

Evidence base

Six RCTs have investigated the use of corticosteroids in acute MS relapses.[2–4] In five, the percentage of patients whose symptoms remained unchanged or deteriorated was much higher with placebo than with corticosteroids. All of four small trials comparing equivalent-dose oral with IV steroids found that oral steroids were non-inferior to IV steroids in terms of efficacy and side effects.

Disease-modifying therapy

Disease modification in RRMS is a rapidly developing field. Several drugs have emerged over the last decade, and there is a healthy pipeline of new agents in development. DMTs, particularly when given early in the disease course, convincingly reduce relapses, MRI activity, and the rate of relapse-dependent and to a lesser degree relapse-independent accumulation of disability. Efficacy of DMTs is measured in terms of impact on relapses (annualized relapse rate (ARR), time to next relapse, risk of relapse) and on disability accumulation (increase in disability as measured by the Expanded

Disability Status Scale (EDSS), sustained for 3 or 6 months). Impact on MRI indicators of disease activity (new and enlarging T2 lesions, gadolinium-enhancing lesions, total lesion load) and axon loss or progression (T1 lesion volume, total brain volume, spinal cord volume) is also considered. The concept of disease-free status or 'no evidence of disease activity' (NEDA) is calculated using a combination of these parameters and is considered an aspirational treatment target.

MS DMTs are often divided in terms of efficacy into 'low efficacy' [β interferons (βIFN), glatiramer acetate (GA) and teriflunomide], 'medium efficacy' (fumarates, S1P receptor modulators) and 'high efficacy' agents (cladribine, natalizumab, CD20 mAbs, and alemtuzumab)—see Table 6.1.

Low efficacy platform therapies

The injectable DMTs (βIFN and GA) have a modest effect on clinical and MRI indices of MS activity in RRMS and excellent long-term safety. In established RRMS, these drugs reduce relapse rate by ~30%, with a similar effect on relapse-associated accumulation of disability.[5–9] There is increasingly compelling evidence that treatment initiated early in the course of the disease, after the first clinical event (clinically isolated syndrome), may be even more beneficial,[10] and most clinicians would offer first-line DMTs after a single clinical event. An oral therapy, teriflunomide has similar efficacy to β IFN and GA, and a favourable side effect profile.[11,12]

Moderate efficacy oral therapies

The sphingosine-1-phosphate (S1P) receptor modulators fingolimod, ponesimod, siponimod, and ozanimod demonstrate greater efficacy than the platform therapies, reducing MS activity by 50–60%.[13–15] Due to the risk of first-dose bradycardia with fingolimod, observation and cardiac monitoring for 6 h is required following treatment initiation. In the UK, National Institute for Health and Care Excellence (NICE) approval has been granted for second-line therapy only, but it is used first-line elsewhere. More selective S1P receptor modulators, ozanimod, ponesimod, and siponimod have similar efficacy but fewer cardiac side effects. S1P receptor modulators are approved by the EMA for RMS, and by the FDA for RMS, CIS, and active SPMS.[16,17,18] Siponimod is the only S1P receptor modulator licensed by EMA for active SPMS.

Oral dimethyl fumarate (DMF) and diroximel fumarate (DRF) also show superior efficacy to the platform therapies, and are well tolerated.[19,20]

High-efficacy therapies

The monoclonal antibodies natalizumab, ocrelizumab, ofatumumab, rituximab and alemtuzumab reduce MS activity by 70–80%. Natalizumab (anti-α4 integrin) is given by infusion every 4–6 weeks, and works quickly, but its long-term use is limited by the rare but serious side effect of progressive multifocal leukoencephalopathy (PML).[21,22] Risk of PML can be stratified by the presence of JC virus antibodies, which should be evaluated prior to initiation of natalizumab and every 6 months on treatment. Ocrelizumab (anti-CD20) is given by infusion every 6 months[23] and ofatumumab, (anti-CD20), is given by SC injection every 4 weeks.[24] Alemtuzumab (anti-CD52) is an induction therapy administered in two IV courses one year apart,[25,26] but vascular side effects have consigned its use to 2nd or 3rd line. Rituximab (anti-CD20) is used extensively off-label in Sweden and elsewhere.[27,28]

Table 6.1 MS disease-modifying therapies

DMT	Mechanism	Form	Efficacy	Common or serious side effects	Pivotal trials
Interferon-β (βIFN) βIFN-1a Avonex®, Rebif®, Plegridy®) βIFN βIFN-1b (Betaseron®/ Betaferon®, Extavia®)	Multiple effects, immunomodulatory. Antiviral. Alters balance of pro- and anti-inflammatory agents and reduces the passage of immune cells through BBB	Rebif® 44 mcg 3x/week Betaseron®/ Betaferon®/Extavia® 250 mcg (8 million IU) SC alt days Plegridy® 125 mcg SC fortnightly Avonex® 30 mcg IM 1×/ week	LOW 30% ↓ ARR c.f. placebo 2. NEDA 13–29% 31% ↓ CDP at 10 y	Injection site reactions Flu-like symptoms Depression, hepatotoxicity Rare hypersensitivity reactions Rare bone marrow suppression	PRISMS 1999 IFNB MSSG 1993 MSCRG 1996 ADVANCE 2014
Glatiramer acetate (Copaxone®, Brabio®, Glatopa®)	Multiple effects, immunomodulatory. Synthetic polypeptide mimicking myelin switches T cells and cytokines from pro- to anti-inflammatory phenotype	20 mg SC QD or 40 mg SC 3×/week	LOW 30% ↓ ARR cf placebo 31% ↓ CDP at 10 y	Injection site reactions Rare infusion reactions	Copolymer 1 MSSG 1995
Teriflunomide (Aubagio®)	DHOD inhibitor (inhibits pyrimidine synthesis, antiviral, anti-proliferative, immunoregulatory, and immunomodulatory effects)	Oral 14 mg od	LOW 31.5–36% ↓ ARR cf placebo 20.2% ↓ CDP at 2 y	Gastrointestinal Hepatotoxicity Alopecia Headache Teratogenic	TEMSO 2011 TOWER 2014

(Continued)

Table 6.1 *(Contd.)*

DMT	Mechanism	Form	Efficacy	Common or serious side effects	Pivotal trials
Fumarates Dimethyl fumarate (Tecfidera®) Diroximel fumarate (Vumerity®)	Activates nrf-2 signalling pathway. Reduces cytotoxic effects of oxidative stress (downregulates NFkB). May modulate proinflammatory pathways	Oral Dimethyl fumarate 240 mg bd Diroximel fumarate 462 mg bd	MEDIUM 44–53% ↓ ARR c.f. placebo 38% ↓CDP at 2 y 2. NEDA 28%	Gastrointestinal Flushing, rash Hepatotoxicity Lymphopenia PML (very rare, after prolonged lymphopenia)	DEFINE 2012 CONFIRM 2012
S1P receptor modulators Fingolimod (Gilenya®) Ozanimod (Zeposia®) Ponesimod (Ponvory®) Siponimod (Mayzent®)	S1P receptor modulator. Prevents lymphocyte egress from lymphoid tissue. Also, probable direct effect on CNS resident immune cells	Oral Fingolimod 0.5 mg od Ozanimod 0.92 mg od Ponesimod 20 mg od Siponimod 1–2 mg od	MEDIUM Fingolimod 48–54% ↓ ARR c.f placebo at 2 y; 17–30%↓3-month CDP at 2 y 2. NEDA 38% 52% ↓ ARR cf βIFN 29%↓3-month CDP at 2 y c.f. βIFN Ozanimod 38–48% ↓ ARR c.f. βIFN	First-dose bradycardia Atrioventricular block Headache Hepatotoxicity Macular oedema Basal cell carcinoma PML (rare)	Fingolimod FREEDOMS I 2010 FREEDOMS II 2014 TRANSFORMS 2010 Siponimod EXPAND 2018 Ponesimod OPTIMUM 2021 Ozanimod SUNBEAM 2019 RADIANCE 2019

DMT	Mechanism	Form	Efficacy	Common or serious side effects	Pivotal trials
Cladribine (Mavenclad®)	Synthetic purine nucleoside analogue. Antimetabolite selective for B and T lymphocytes causing apoptosis *Immune reconstitution therapy*	Oral induction course totalling 3.5 mg/kg 10–20 mg daily for 5 days, repeated months 2, 13, and 14	HIGH 57.6% ↓ ARR at 2 y cf placebo 47% ↓CDP at 2 y (all) HIGH in highly active MS 67% ↓ ARR at 2 y c.f. placebo 2. NEDA 46–48%	Lymphopenia → infections, oral herpes, and shingles Headache URTI TB reactivation (rare)	CLARITY 2010 CLARITY EXTENSION
Natalizumab (Tysabri®)	Anti—α4 integrin humanized IgG4 monoclonal antibody. Blocks passage of activated T cells through BBB into CNS)	IV infusion 300 mg over 1 hour, monthly	HIGH 68% ↓ ARR c.f. placebo 50–60% ↓ ARR c.f. βIFN 42% ↓ CDP at 2 y 2. NEDA 37%	PML—infusion reactions (usually mild)	AFFIRM 2006 SENTINEL 2006
Ocrelizumab (Ocrevus®)	Anti-CD20 humanized IgG monoclonal antibody (B cell ablation)	IV infusion 600 mg over 2–3.5 hours, every 6 months	HIGH 47% ↓ ARR cf βIFN 96-week NEDA 48% cf βIFN 30%	Infusion reactions Viral infections RTIs, skin, and sinus infections TB/Hep B reactivation Hypogammaglobulinaemia → infections	OPERA I 2017 OPERA II 2017

(Continued)

Table 6.1 (*Contd.*)

DMT	Mechanism	Form	Efficacy	Common or serious side effects	Pivotal trials
Ofatumumab (Kesimpta®)	Anti-CD20 recombinant fully human IgG1 monoclonal antibody (B cell ablation)	SC 20 mg every 4 weeks	HIGH 50.5% and 58.5%↓ARR c.f. teriflunomide 34.4%↓3 mo CDP at 33 mo 32.5%↓6 mo CDP at 33 mo	Injection related reactions (mild, esp first dose) Nasopharyngitis Headache RTI, UTI TB/Hep B reactivation	ASCLEPIOS I 2020 ASCLEPIOS II 2020
Alemtuzumab (Lemtrada®)	Anti-CD52 monoclonal antibody (activated T and B cell ablation). Depletes mature T and B cells with subsequent complex reorganization of immune repertoire as immune system reconstitutes *Immune reconstitution therapy*	IV infusion 12 mg every day for 5 days, repeated for 3 days after 12 months	HIGH 70–80% ↓ ARR c.f. placebo 49–55% ↓ ARR c.f. βIFN 42%↓CDP at 2 y 2. NEDA 39–32%	Infusion reactions Autoimmunity – ITP, thyroid, renal Rash Zoster, Listeria, RTI, UTI Arterial dissection, stroke (rare)	CARE-MS1 2012 CARE-MS2 2012
Autologous haematopoietic stem cell therapy (AHSCT)	IRT—Chemical bone marrow ablation followed by stem cell reconstitution. *Immune reconstitution therapy*		HIGH Total suppression of relapses Disability static or improved in the majority 2. NEDA 78–93.3% 5. NEDA 69.2% No new T2 or gd+ lesions at 4 y	Mortality approx. 1% (reducing to 0.2% in last 5 years)	

ARR, annualized relapse rate; BBB, blood–brain barrier; CDP, confirmed disability progression; DHOD, dihydro-orotate dehydrogenase; NRF, nuclear respiration factor; NEDA, no evident disease activity; S1P, sphingosine-1-phosphate.

Cladribine, a novel oral induction therapy which induces lymphocyte apoptosis, has similar efficacy to the monoclonal antibodies in rapidly evolving severe MS,[29,30] and is convenient and well tolerated.

DMT choice—general principles

Choice of DMT is made jointly, taking into account patient preference, and influenced by prognostic factors including disease activity (number of relapses, interval between relapses, severity of and degree of recovery from relapses), degree of disability, disease duration, MRI appearances (total T2 lesion load, presence or absence of infratentorial or spinal cord lesions, new/enlarging lesions, gadolinium-enhancing lesions) and comorbidities including serologic evidence of prior exposure to JC virus, tuberculosis, and viral hepatitis. In the UK, DMT choice is guided by the NHS England Disease Modifying Therapy Algorithm,[31] which restricts use of higher efficacy therapies to those with more active disease.

There is increasing awareness of the importance of early treatment, and an ongoing debate about the respective merits of giving highly effective and/or immune reconstitution therapies early, or starting with moderately effective agents and escalating to stronger agents in the event of new disease activity, with evidence increasingly favouring early treatment with high efficacy agents.

Until recently there were no licensed treatments for people with SPMS or PPMS, with the exception of βIFN for SPMS with ongoing relapses. However many of the DMTs licensed for RRMS have been shown over time to reduce long-term disability accrual, at least a proportion of which is likely to be relapse-independent. Ocrelizumab has received FDA and EMA approval for use in active PPMS,[32] and siponimod has been licensed for use in active SPMS.[33] Ozanimod and ofatumumab are licensed for active SPMS by the FDA but not the EMA.[16,17,24] The presence of ongoing relapses, or an active MRI (new/enlarging T2 lesions or gadolinium-enhancing lesions) is required to qualify for these treatments. All agents modestly reduce the rate of clinical disability progression by 20–30% over 2–3 years.

Neuro-protection is a focus of current research, and several agents are undergoing evaluation in clinical trials. Repair and remyelination strategies are also at early stages of development.

Autologous haematopoetic stem cell transplantation (AHSCT)

Detailed discussion of AHSCT is beyond the scope of this book but the authors direct the reader to a comprehensive review article.[34] AHSCT is an intensive anti-inflammatory and immunomodulatory therapy with significant short-term toxicity. Younger patients, shorter duration of disease, lower EDSS scores, active inflammatory disease, and absence of comorbidities have been associated with more favourable outcomes. It is considered in patients with highly active disease failing at least one DMT, fulminant aggressive MS, and less commonly progressive MS with an active inflammatory component. Rates of NEDA in appropriately selected patient groups are superior to DMTs (see Table 6.1) but safety remains a concern.

Evidence base for DMTs

Low efficacy agents—βIFNs, GA, teriflunomide

The βIFN preparations (once-weekly IM βIFN-1a, thrice-weekly SC βIFN-1a, alternate day SC βIFN-1b, and fortnightly SC pegylated βIFN-1a) all demonstrated comparable efficacy in pivotal double-blind, phase 3 randomized placebo-controlled clinical trials. Broadly, ARR was reduced by 30% and MRI indicators of activity were significantly reduced[5–10] over 2 years. The Copolymer MS Study Group found similar results for glatiramer acetate with 29% reduction in ARR over 2 years. Several long-term follow-up studies subsequently confirmed a positive impact of βIFN and GA on disability progression including the UK Risk Sharing Scheme,[9] which demonstrated that βIFN and GA slowed the rate of EDSS worsening by 31% over 10 years of follow-up when compared to an untreated cohort obtained from natural history studies. Beta-interferons are licensed for use in active SPMS as well as relapsing MS.

In TEMSO, teriflunomide reduced ARR by 31.5% and CDP by 20.2% compared with placebo over 2 years. MRI activity was also significantly reduced in the treatment group.[11] In TOWER, ARR was reduced from 0.50 in placebo to 0.32 in the teriflunomide group, and the risk of sustained CDP was significantly reduced, with a hazard ratio of 0.68).[12]

Medium efficacy DMTs – SIP receptor modulators and fumarates

Fingolimod was investigated in two placebo-controlled RCTs, FREEDOMS I and II.[14,15] In both trials ARR was reduced at 12 months by 54% and 48% respectively compared to placebo, and 3-month and 6-month CDP was reduced from 24.1% and 19% in the placebo groups to 17.7% and 12.5% in the treatment groups. There were also significant reductions in MRI new/enlarging T2 lesions, gadolinium-enhancing lesions, and brain volume loss in the treated groups. Comparison of fingolimod with IM βIFN-1a in the TRANSFORMS study[13] showed a reduction in ARR from 0.33 in the IM βIFN-1a group to 0.16 in the fingolimod-treated group after 12 months.

Similar results were demonstrated with ozanimod.[16,17] In the SUNBEAM trial, at 12 months the ARR was reduced by 48% and MRI activity reduced by 63% with ozanimod, compared with IM βIFN-1a. In the RADIANCE trial, ARR was reduced by 38% at 2 years, and there was a 42% reduction in new/enlarging T2 lesions, 53% reduction in gadolinium-enhancing lesions and 25% reduction in whole brain volume loss in the ozanimod group versus IM βIFN-1a. No significant differences in CDP were seen but rates were low in both groups. In the EXPAND trial of siponimod in SPMS,[18] siponimod delayed disability progression by 26% compared to placebo. Subgroup analysis revealed a greater beneficial effect (37% reduction in CDP) in patients with active SPMS (those with superimposed relapses or new/enlarging T2 lesions or gadolinium-enhancing lesions on MRI). In the ASCLEPIOS I and II RCTs,[24] ofatumumab 20 mg SC every four weeks was compared with daily oral teriflunomide in patients with RRMS or active SPMS. Ofatumumab demonstrated 50.5% and 58.5% reductions in ARR after 33 months, as well as reduction in 3-month CDP by 34.4% and 6-month CDP by 32.5%. Ofatumumab also resulted in 97.5% and 93.8% fewer gadolinium-enhancing lesions compared with teriflunomide.

Siponimod, ozanimod and ofatumumab have been licensed to treat active SPMS as well as relapsing MS in USA in light of the positive outcomes in patients with active SPMS in these trials.

In the DEFINE study[19] dimethyl fumarate significantly reduced the proportion of patients who relapsed by 49%, the AAR by 53%, and 3-month CDP by 38% relative to placebo at 2 years. In the CONFIRM study,[20] Dimethyl fumerate (DMF) reduced AAR by 44% and the proportion of patients who relapsed by 34% compared with placebo at 2 years.

High efficacy DMTs—monoclonal antibodies and cladribine

The SENTINEL study[21] investigated the addition of natalizumab to βIFN-1a over two years, in people with ongoing relapses despite weekly IM βIFN-1a. Addition of natalizumab resulted in a 24% reduction in risk of CDP, and a 54% reduction in ARR (from 0.75 to 0.34). There were also 83% fewer new/enlarging T2 lesions and an 89% reduction in gadolinium-enhancing lesions in the natalizumab treated group. However, 2 patients treated with natalizumab developed PML, one with fatal outcome. In the AFFIRM study[22] natalizumab monotherapy was compared to placebo over two years. Natalizumab led to a 68% reduction in ARR, a 42% reduction in CDP, an 83% reduction in new/enlarging T2 lesions, and 92% fewer gadolinium-enhancing lesions.

CARE-MS1 and CARE-MS2 RCTs[25,26] compared alemtuzumab (five consecutive daily infusions followed 12 months later with 3 infusions) with 3xweekly SC βIFN-1a. Alemtuzumab produced 54.9% and 49.4% reduction in relapses compared with βIFN-1a, and 42% reduction in CDP was seen with alemtuzumab in CARE-MS 2. A high incidence of thyroid dysfunction and other autoimmune conditions in the alemtuzumab-treated groups was noted in both trials.

In HERMES,[27] a phase II study of rituximab versus placebo the primary endpoint was comfortably met with a 91% reduction in gadolinium-enhancing lesions. Key secondary endpoints of relapse reduction were also met. Despite these encouraging results, no phase 3 study was ever undertaken for commercial reasons, and other anti-CD20 therapies were developed instead. The OPERA I and II studies[23] compared ocrelizumab infusions every 6 months with SC βIFN-1a three times weekly over 2 years. Ocrelizumab resulted in 46% and 47% reduction in ARR, and 3-month CDP was reduced from 13.6% to 9.1%, and 6-month CDP from 10.5% to 6.9%. MRI gadolinium-enhancing lesions were reduced by 94% and 95% in the ocrelizumab-treated groups. Preliminary results from a 3-year open-label extension study show a sustained beneficial effect of ocrelizumab on relapse suppression. The ORATORIO trial[34] examined the effect of ocrelizumab on disease course in PPMS. There was a 24% reduction in 3-month CDP and 25% reduction in 6-month CDP in the ocrelizumab group compared to placebo, as well as 29.3% reduction in timed 25-foot walk worsening over 2.9 years. In addition, there was less accumulation of T2 lesions, and slower rates of brain volume loss in the treated group. The beneficial effects of ocrelizumab were greater in younger patients with shorter disease duration and active lesions on MRI.

The CLARITY RCT[29] compared two different doses of cladribine (3.5 mg/kg and 5.25 mg/kg cumulative doses), given as short-course oral induction therapy, against placebo. Cladribine treatment resulted in 57.6% reduction in ARR, 33% reduction in 3-month CDP, 85.7% fewer gadolinium-enhancing lesions and 73.4% reduction in new/enlarging T2 lesions compared to placebo over 2 years. Efficacy was maintained in a 2-year extension study, with 75% of patients remaining relapse-free.[30]

Vitamin D

There is an inverse relationship between sun/ultraviolet B radiation exposure and serum vitamin D levels, and the risk or prevalence of MS. Accumulating data suggest that low serum vitamin D levels increase the risk of developing MS and adversely affect MS disease course. Many clinicians recommend that all people with MS take vitamin D3 (colecalciferol) supplements 2000–4000 IU daily (or 20000 IU every 1–2 weeks), aiming for serum 25-hydroxy vitamin D levels comfortably within the sufficient range (>30 ng/mL or >75 nmol/L).[33]

Fulminant and tumefactive multiple sclerosis

Occasionally, MS presents with an aggressive, fulminant course with rapid accumulation of new lesions and neurological deficits, despite high-dose IV methylprednisolone. There is no strong evidence base to guide management in these unusual circumstances, but plasma exchange (PLEX),[35] natalizumab, cyclophosphamide, and mitoxantrone have been reported to be of benefit. The American Academy of Neurology (AAN) and Association of British Neurologists (ABN) recommend plasmapheresis and early natalizumab for aggressive-onset relapsing MS. Consideration may also be given to Autologous haematopoetic stem cell transplantation (AHSCT) in selected cases.

Treatment of symptoms

Common symptoms caused by MS and their treatments are summarized in Table 6.2. Agents used to treat these symptoms are discussed in detail in the relevant chapters but fampridine for walking impairment, treatment of paroxysmal symptoms of MS, management of fatigue, and treatment of vertigo and oscillopsia will be covered here.

Walking impairment

Fampridine, a slow-release formulation of the voltage-gated potassium channel (VGKC) blocker 4-Diaminopyridine (DAP), has been shown to significantly improve walking speed in approximately one-third of people with MS.[36,37] A timed walk before and after fampridine administration is recommended to objectively ascertain response to treatment, which should be reviewed periodically.

Paroxysmal symptoms of MS

Paroxysmal symptoms are well-recognized manifestations of MS. These are characterized by multiple, stereotyped episodes manifest as short-lasting and highly repetitive motor, sensory, visual, brainstem, or autonomic symptoms. They are thought to be due to ephaptic transmission between partially demyelinated axons.

Table 6.2. Treatment of common symptoms of MS

Symptom	Pharmacologic management	Physical/holistic	Chapter reference
Spasticity	Baclofen, tizanidine, gabapentin Dantrolene, benzodiazepines, cannabinoids	Physiotherapy, stretches Intrathecal baclofen, intrathecal phenol/alcohol Botulinum toxin (focal spasticity)	Spasticity, Chapter 15
Dysaesthesia	Amitriptyline, nortriptyline, gabapentin, pregabalin	Cognitive behavioural therapy, mindfulness	Neuropathic pain, Chapter 5
Neuralgia including trigeminal neuralgia	Carbamazepine, oxcarbazepine, lamotrigine, gabapentin	Decompressive and nerve ablation procedures in refractory cases	Neuropathic pain, Chapter 5
Paroxysmal symptoms (motor, sensory, brainstem/cerebellar)	Na_V channel blockers—carbamazepine, oxcarbazepine Other AEDs—lamotrigine, topiramate, gabapentin, pregabalin Misoprostol, TCAs, opioids	Neuromodulation—transcranial magnetic stimulation, surgical	MS and related disorders, Chapter 6
Depression	SSRIs, SNRIs	Psychotherapy, mindfulness, meditation	n/a
Anxiety	SSRIs, SNRIs	Cognitive behavioural therapy, mindfulness, meditation,	n/a
Storage dysfunction (detrusor hyperactivity/ overactive bladder)	Antimuscarinics +/– mirabegron Intravesicular botulinum toxin Desmopressin Cannabinoids (Europe)	Pelvic floor muscle training Neuromodulation (neuromuscular electrical stimulation, transcutaneous tibial nerve stimulation)	Uro-neurology, Chapter 20

(*Continued*)

Table 6.2. *(Contd.)*

Symptom	Pharmacologic management	Physical/holistic	Chapter reference
Voiding dysfunction (detrusor-sphincter dyssynergia)	Alpha-blockers Desmopressin	Neuromodulation Clean intermittent self-catheterization Indwelling suprapubic catheterization	Uro-neurology, Chapter 20
Bowel dysfunction	Oral laxatives, suppositories, enemas	Diet, fluid, exercise, bowel irrigation systems	Neurogenic bowel dysfunction, Chapter 20
Fatigue	Amantadine, modafanil, methylphenidate, 4-AP, 3,4-DAP, paroxetine, pemoline	Sleep hygiene	MS and related disorders, Chapter 6
Walking	fampridine	Physiotherapy, walking aids, FES	MS and related disorders, Chapter 6
Tremor	Trihexyphenidyl, primidone, propranolol, levo-dopa, levetiracetam, isoniazid	DBS/thalomotomy MRI-guided focused ultrasound thalamotomy Botulinum toxin	Hyperkinetic movement disorders, Chapter 13
Vertigo and oscillopsia	Baclofen, gabapentin, memantine, clonazepam,4-AP, 3,4-DAP	Vestibular rehabilitation/physiotherapy	MS and related disorders, Chapter 6
Erectile dysfunction	PDE5 inhibitors	Vacuum constriction devices Intracavernosal and intraurethral prostaglandin E, penile implants	Uro-neurology, Chapter 20

Specific examples are protean but include dystonic spasms, facial myokymia, hemifacial spasm, weakness (e.g. leg giving way, dropping objects), dysaesthesia, neuralgia, dysarthria/ataxia, vertigo, and diplopia.

Treatment of paroxysmal symptoms

The possibility of an MS relapse should be considered if the symptoms persist for >24 h as there can be a good response to pulsed steroid treatment. Most paroxysmal symptoms respond well to Na_V channel blockers (carbamazepine or oxcarbazepine) or other AEDs including levetiracetam, gabapentin, pregabalin acetazolamide, or clonazepam.[37,38]

Fatigue

Fatigue is commonly experienced in people with MS as an overwhelming feeling of exhaustion and lack of energy. MS-related fatigue differs from physiological fatigue (tiredness) by being more intense and long-lasting, and not relieved by sleep or rest. The cause remains unknown but hypotheses include high levels of proinflammatory cytokines (TNF-α and interferon-γ), endocrine influences (decrease in Dehydroepiandrosterone (DHEA) concentration), axonal loss, and increased compensatory cerebral activation.

Treatment of fatigue

Non-pharmacological strategies include the identification and elimination of fatigue-enhancing factors (alcohol, nicotine, sleep disturbance, overheating), reviewing medication that may aggravate or cause fatigue, and encouraging exercise (with cooling strategies if necessary). Underlying depression should be treated if present.

Many drugs have been tested in the treatment of primary MS fatigue. However, the evidence supporting their effectiveness is scant and of low quality. Studies involving small sample sizes have produced conflicting results. Commonly trialled agents include amantadine, modafanil, 4-aminopyridine, fampridine, paroxetine, acetyl-L-carnitine, pemoline, and methylphenidate.

Vertigo

The vestibular system is frequently involved in MS. Vertigo is seen as an initial presentation in 5% of patients with MS and will ultimately occur in 40% of patients with established MS. Patients usually describe vertigo that is torsional (rotational) but can be in any direction and can be positional. There is often associated spontaneous or positional nystagmus which of a 'central' type. Central type of nystagmus is usually direction changing i.e. right beat in right gaze and left beat in left gaze. There may also be gait and limb ataxia, dysarthria, and slow pursuit movements related to cerebellar dysfunction.

Management of central vertigo is discussed in Chapter 2, vertigo but medications that may be helpful in MS patients with vertigo include meclizine, low-dose diazepam, and promethazine hydrochloride.

It is important to remember that Benign Paroxysmal Positional Vertigo (BPPV) remains the commonest cause of vertigo and imbalance, irrespective of any coexisting neurological syndrome. Thus, vertigo should not be automatically attributed to demyelination in a patient with MS.

Nystagmus and oscillopsia

Drug treatment of oscillopsia and vertigo caused by nystagmus is rarely effective and there are no licensed treatments. Limited success has been reported in small case series of baclofen, gabapentin 1200 mg daily, memantine 40–60 mg daily and clonazepam 0.5–1 mg bd. Whether one drug or another is more effective is idiosyncratic, but all are reasonably well tolerated. Anticholinergic agents, such as trihexyphenidyl and transdermal scopolamine are not effective treatments. The potassium channel blockers 4-aminopyridine and 3,4-diaminopyridine have been reported to improve vertical nystagmus, gait, and limb ataxia in small case studies

Related CNS inflammatory disorders

Neuromyelitis optica spectrum disorder (NMOSD)

Neuromyelitis optica spectrum disorder (NMOSD), previously known as Devic's disease, is characterized by optic neuritis, often bilateral, sequential and severe, and longitudinally extensive transverse myelitis (LETM –>3 vertebral segments). Since the discovery of antibodies against aquaporin 4 (AQP4-IgG), a water channel abundant in the CNS, it is clear that clinical presentations can be more diverse, and the term NMO spectrum disorder (NMOSD) is now used in preference.[39]

International consensus diagnostic criteria were published in 2015.[39] In patients with AQP4-IgG, the diagnosis only requires one of the six core clinical criteria. In patients without AQP-4 IgG, diagnosis requires two core clinical characteristics disseminated in space, at least one of which must be myelitis, optic neuritis, or area postrema syndrome (hiccups, nausea, vomiting).

Core clinical characteristics of NMOSD:

1. optic neuritis
2. acute myelitis (with LETM on MRI)
3. area postrema syndrome (with dorsal medulla/area postrema MRI lesions)
4. acute brainstem syndrome (with peri-ependymal brainstem MRI lesions)
5. narcolepsy, or acute diencephalic clinical syndrome (with typical diencephalic MRI lesions)
6. symptomatic cerebral syndrome (with typical brain MRI lesions)

Untreated, there is high early morbidity and mortality from severely disabling attacks, often leading to permanent disability. In a minority, the disease is monophasic. There is no progressive phase of the sort seen in MS, but major relapses are common. Because disability accumulates as a direct consequence of relapses that typically leave substantial residual disability, early relapse recognition and aggressive treatment is crucial. Importantly, several treatments that are effective in MS, including βIFN, fingolimod, alemtuzumab, and natalizumab, have been associated with catastrophic exacerbations in patients with NMOSD.

Management of NMOSD

Treatment of acute relapses

- Corticosteroids—IV methylprednisolone 1 g daily for 3–5 days, followed by PO prednisolone 0.75–1 mg/kg daily (often 15–30 mg), +/– oral taper over several weeks.
- Concomitant PLEX.

Maintenance immunotherapy

First line (in order of preference):

Rituximab 1000 mg two weeks apart repeated every 6–12 months depending on CD19 suppression – retreat when CD19 >0.05% total lymphocyte count in first 2 years, and >0.1% thereafter.

OR

Mycophenolate mofetil (MMF) 1 g bd (maximum 1.5 g bd) plus low-dose prednisolone (prednisolone gradually tapering until discontinued) – aiming for target lymphocyte count <0.5.

OR

Azathioprine (2–3 mg/kg/day), initially with low-dose prednisolone.

Second line: *

Rituximab for MMF and azathioprine failures; methotrexate 15–25 mg once weekly, cyclophosphamide, mitoxantrone.

* New agents may be used second line depending on national and local funding and guidelines—satralizumab, inebilizumab, eculizumab, tocilizumab.

Remission can usually be achieved promptly with corticosteroids, and PLEX is usually given concomitantly in view of the high risk of significant residual disability from under-treated relapses.

Most patients can be kept relapse-free with long-term immunosuppression. Rituximab has been used off-label for years and has been promoted to first-line use in view of gradually emerging data on superior efficacy. European Federation of Neurological Societies (EFNS) guidelines in 2010 recommended first-line therapy with either rituximab or a combination of azathioprine and prednisolone, but mycophenolate has since shown higher efficacy than azathioprine so is generally used in preference to azathioprine.

Six randomized-controlled prospective studies have been published in 2019/20 involving five different monoclonal antibodies. Rituximab and tocilizumab are being used off-label, and eculizumab, satralizumab and inebilizumab were approved for use by FDA and EMA in 2019/20. In AQP4 sero-positive patients, monoclonal antibodies that deplete B cells (rituximab and inebilizumab), interfere with interleukin 6 signalling (tocilizumab and satralizumab) or disrupt complement activation (eculizumab) have superior efficacy compared to placebo. Rituximab, tocilizumab and to some extent eculizumab have well-known safety profiles, and rituximab and azathioprine may be safe during pregnancy. A treatment algorithm including these new agents has yet to be developed.

Evidence base—acute management

Several recent retrospective studies have demonstrated improved outcomes with early PLEX. The probability of complete recovery decreased from 50% with immediate PLEX, to 1–5% with delayed PLEX (after day 20), and in another, immediate initiation of apheresis (within 2 days of symptom onset) was associated with a 40% rate of complete response compared with 3.2% when started at day 6, emphasizing the importance of early treatment.[40] Several other studies have demonstrated the superiority of Intravernous Methylprednisolone (IVMP) combined with PLEX over IVMP alone.[41] Data on the use of IVIg for NMO relapses are limited, although small studies indicate it may be effective in preventing relapses.

Evidence base—maintenance immunotherapy

Modern maintenance treatment of NMOSD has been based on open-label prospective and retrospective case series and consensus reports.

The use of low-dose corticosteroids for maintenance treatment is supported by retrospective evidence, but has not been studied systematically.

The best-studied immunotherapies are rituximab, mycophenolate mofetil (MMF), and azathioprine. Rituximab decreased relapse rate by up to 88%, with 2/3 patients achieving complete remission during a 10-year study, whereas MMF reduced relapse rate by 87.4% with a 36% failure rate and azathioprine reduced relapse rate by 72% with a 53% failure rate, even when used concurrently with prednisone.

In RIN-1, a multicentre, double-blind RCT of 38 patients with seropositive NMOSD taking prednisolone maintenance therapy, 19 patients were randomized to rituximab and 19 to placebo infusions. Rituximab caused complete suppression of relapses during the 72-week study period, whereas 37% of placebo-treated patients experienced relapses.[42]

Most evidence for azathioprine in NMOSD has come from retrospective case series. These, and one open clinical trial suggest that azathioprine is effective but inferior to rituximab and MMF.

Mitoxantrone, methotrexate, cyclophosphamide, and cyclosporin A have been shown to be of some benefit in small studies but use has been limited due to side effects and teratogenicity.

In the PREVENT study, an open-label phase 3 double-blind RCT of eculizumab, a C5 complement-blocking monoclonal antibody, 143 patients with AQP4+ NMOSD taking background immunosuppressants were randomized 2:1 to eculizumab or placebo[43] as add-on therapy. 97.9% and 96.4% of the eculizumab-treated group remained relapse-free after 2 years and 4 years, respectively, compared to 63.2% and 51.9% of the placebo group.

Two open-label trials of tocilizumab, a humanized anti-IL6 receptor monoclonal antibody, demonstrated a reduction in relapse rates in patients with AQP4$^+$ NMOSD, refractory to background immunotherapy, as adjunctive treatment or monotherapy. In one trial involving 7 patients, ARR fell from 2.9 to 0.4. In the other, ARR fell from 4.0 to 0.4 in 8 patients after treatment with tocilizumab. The TANGO trial[44] involved 118 patients randomly allocated 1:1 to tocilizimab (8 mg/kg IV every 4 weeks) or azathioprine (2–3 mg/kg daily) and demonstrated superiority of tocilizumab over azathioprine in relapse suppression, in that 14% of the tocilizumab-treated group compared to 47% of the azathioprine group had relapses at 60 months.

SAKuraSky,[45] a randomized, international, double-blind phase 3 trial of satralizumab as adjunctive therapy (n = 83; 1:1 randomization to satralizumab or background immunosuppressant) showed satralizumab reduced the risk of relapse by 62% in all patients with NMOSD; AQP4+ patients (n = 53) had a 79% relapse risk reduction and AQP4-patients (n = 30) a 34% risk reduction. By the end of the study at 2 years, 91.5% of the AQP4+ patients treated with satralizumab were relapse-free compared with 53.3% of those taking background immunosuppressant alone. In SAKuraStar,[46] a multicentre, double-blind placebo-controlled phase 3 trial, 95 NMOSD patients were allocated 2:1 to satralizumab or placebo. Satralizumab treatment resulted in a 74% relapse reduction, 76.5% of the treated group compared to 41.1% of the placebo group remaining relapse-free at 2 years.

Finally, in the N-MOmentum trial,[47] a phase 3 clinical trial during which 230 patients were randomized 3:1 to inebilizumab 300 mg IV day 1 and 15 only or placebo, inebilizumab treatment reduced the risk of relapse by 73% (77.3% if AQP4+) compared with treatment with placebo.

MOG antibody disease (MOGAD)

Some patients with presentations resembling NMOSD or MS have antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG), and MOGAD has now been recognized as a distinct clinical entity. It is characterized by optic neuritis (unilateral or bilateral, often involving the anterior segment with perineural enhancement on MRI), transverse myelitis which is often severe and is longitudinally extensive in ~60% cases. The conus is commonly involved and many exhibit the characteristic H sign on axial imaging. Another common presentation is with ADEM or cortical encephalitis, or less often a brainstem syndrome (typically pontine or thalamic). Diagnosis requires the presence of anti-MOG-IgG in serum. The course is monophasic in about 50%, and a relapsing course may be predicted by persistently high levels of MOG-IgG. International consensus diagnostic criteria are being developed.

Management of MOGAD

Treatment of acute relapses

First line: IVMP 1 g daily for 3–5 days with oral prednisolone taper over 3–6 months

Second line: prompt PLEX if severe or refractory; IVIg possible alternative to PLEX

Relapse prevention*

Consider low-dose oral prednisolone, periodic IVIg, MMF, rituximab, azathioprine, or tocilizumab.

*NB approximately 50% patients may have a monophasic illness so the need for long-term immunosuppression has not been determined and is generally considered in those with a relapsing course and/or persistently elevated MOG-IgG levels or a severe initial presentation

Evidence base

There are very little evidence-based data for the treatment of MOGAD because it is a recently recognized entity.[41] However acute treatment with high-dose corticosteroids is usually effective. Given the presence of circulating, presumably pathogenic, antibodies, the treatment approach is aligned with NMOSD rather than MS. A multinational study of 102 children with MOGAD found that treatment with βIFN and GA did not improve the ARR, whereas a significant reduction in ARR was seen with azathioprine (ARR 1.84–1.01), MMF (ARR 1.79–0.52), and rituximab (ARR 2.16–0.51). Several retrospective and prospective observational studies support the use of periodic IVIg, maintenance low-dose corticosteroids, mycophenolate, rituximab, and tocilizumab.[48]

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the CNS that typically follows a febrile infection or a vaccination in children and young adults. There is usually acute or subacute onset of meningism, encephalopathy, and multifocal CNS deficits. Optic nerve involvement, when present, is typically bilateral. MRI shows scattered areas of CNS demyelination. It is usually monophasic, and spontaneous recovery generally begins within a few weeks, with complete resolution in 2–6 months. Controversy exists over the potential risk of subsequent development of MS or NMO. A proportion of cases have positive MOG-IgG.

Acute haemorrhagic leukoencephalopathy (AHLE) is a rare form of severe fulminant ADEM, distinguished only by the presence of severe MRI changes, including haemorrhages, a more aggressive course, and poor outcome, despite intensive immunotherapy and treatment to control raised intracranial pressure.

Multifocal inflammatory leukoencephalopathy due to drugs such as levimasole, and toxic leukoencephalopathies secondary to drugs of abuse (including heroin, cocaine, MDMA), environmental toxins (including toluene, carbon monoxide, lead), therapeutic drugs (cancer chemotherapy, immunomodulators) and radiation, should be considered in the differential diagnosis of ADEM.

Treatment

- *First line*: IV methylprednisolone 20–30 mg/kg/day (maximum 1 g daily) for 3–5 days ± PO prednisolone taper over 3–6 weeks.
- *Second line*: IVIg 2 g/kg over 2–5 days or PLEX.

Empirical antibacterial and antiviral treatment is indicated, until an infectious disease process is ruled out. Cases with limited response to steroids should be treated early with IVIg, which may be given as first-line treatment, instead of steroids, if infectious meningoencephalitis cannot be definitely excluded. PLEX should be given early in severe or resistant cases.

Evidence base

There is a lack of evidence-based, prospective clinical trial data for the management of ADEM. Small published case series support the benefit of corticosteroids and IVIg, as do a limited number of controlled clinical trials. There are no specific recommendations for the long-term management of severe refractory or recurrent/multiphasic ADEM, but rituximab, ciclosporin, and cyclophosphamide have been given, with some success.

Site-restricted inflammatory diseases

Transverse myelitis

Transverse myelitis (TM) is a clinical syndrome with multiple potential causes. Infections precede approximately two-thirds of cases, and post-infectious autoimmune mechanisms are likely to be responsible for the majority, although direct infection can also play a role. TM also occurs in the setting of MS, NMO, MOGAD, and a variety of systemic autoimmune conditions.

Treatment

- *First line*: IV methylprednisolone 1 g daily for 3–7 days.
- *Second line*: PLEX.
- *Third line*: cyclophosphamide, mitoxantrone, rituximab.

Once infection has been ruled out, acute treatment is with high-dose corticosteroids. If response is suboptimal, PLEX should be given (1.5 plasma volumes in five treatments over 10 days), ideally within 2 weeks of onset, although its efficacy has been demonstrated if given within 2 months. Severe or treatment-resistant cases may rarely be treated with cyclophosphamide, mitoxantrone, or rituximab, without good evidence base. Underlying conditions, such as MS, NMO, and MOGAD, should be identified and treated, as appropriate.

Evidence base

There are no RCTs to support the use of methylprednisolone for TM, despite considerable positive clinical experience and several small observational studies confirming its benefit. The efficacy of PLEX has been demonstrated by RCTs in severe and steroid-unresponsive TM. Several small series support the use of cyclophosphamide in severe cases.

Optic neuritis

Optic neuritis may occur as a monophasic condition with no subsequent neurological sequelae. However, there is an estimated lifetime risk of developing MS of up to 50%. The presence of brain MRI lesions at the time of presentation of optic neuritis conveys a greater risk of developing MS compared to those with normal MRIs. Other underlying disorders to be considered at presentation are NMOSD, MOGAD, and an important differential is ischaemic optic neuropathy. In most cases, optic neuritis improves spontaneously without treatment, but if severe or bilateral, treatment with high-dose corticosteroids is appropriate.

Treatment of optic neuritis

- *First line (if clinically indicated)*: IV methylprednisolone 1 g daily for 3 days, or PO methylprednisolone 500 mg to 1000 mg daily for 5 days.
- *Second line*: consider PLEX for severe and/or bilateral visual loss unresponsive to corticosteroids.

Treatment of typical forms of optic neuritis with high-dose corticosteroids shortens the period of acute visual dysfunction but does not affect the final visual outcome. However, the majority of cases do not require treatment, particularly in view of the small, but not insignificant, risk of avascular necrosis of the hip associated with high-dose steroid treatment.

Evidence base

The Optic Neuritis Treatment Trial (ONTT),[49] in alignment with several small studies, found that IV methylprednisolone resulted in faster recovery of visual function, compared with placebo. Controversially, results from the ONTT also suggested that IV methylprednisolone treatment reduced the subsequent risk of recurrent optic neuritis and conversion to MS, and that relatively low-dose PO prednisolone treatment led to increased risk of a second episode. These findings have never been replicated, and the general consensus is that corticosteroid treatment for optic neuritis has no impact on the subsequent risk of developing MS or recurrent optic neuritis. In a Cochrane database review,[50] a meta-analysis of trials evaluating high-dose steroid treatment found no conclusive evidence of long-term benefit in terms of recovery to normal visual acuity, visual field, or contrast sensitivity with either IV or PO corticosteroids.

A study of 34 patients with steroid-resistant, severe optic neuritis found that PLEX led to functionally important visual recovery in more than half of the patients.[51]

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Chapter 7

Other inflammatory disorders of the central nervous system (CNS)

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Introduction

Autoimmune inflammatory mechanisms are increasingly implicated in the pathogenesis of a wide range of neurological diseases.

General principles of immunotherapy

In general terms, immunotherapy for neurological autoimmune diseases varies depending on the disease being treated, its severity, the mechanism of the aberrant immune response, patient co-morbidities, response to prior treatments, and current guidelines for best treatment. However, the overall therapeutic approach is similar and involves initial control of inflammation, followed by maintenance of remission.

Induction of remission

Corticosteroids are very effective at rapidly reducing inflammation and are widely used. They are initially given at high doses to control disease, then tapered to reduce the risk of side effects. Conditions in which circulating autoantibodies are pathogenic generally respond to treatments targeting B cells or interfering with antibody–antigen interactions such as IV immunoglobulin (IVIg) and plasma exchange (PLEX).

Maintenance immunotherapy

Low-dose corticosteroid maintenance may be required and may be substituted or supplemented by immunosuppressants with a slower onset of action but more acceptable long-term side effects. Steroid-sparing immunosuppressants commonly used in neurology include azathioprine, methotrexate, mycophenolate, and cyclophosphamide. Antibody-mediated diseases are generally treated with agents which preferentially target B cells, such as rituximab and ocrelizumab and, in preference to agents with more general immunosuppressant activity. Biological therapies, which target specific components of the immune system, are beginning to replace traditional immunotherapy but are expensive.

Vasculitides affecting the CNS

Primary angiitis of the central nervous system

Primary angiitis of the CNS (PACNS) is a rare condition in which inflammation of small to medium arteries is restricted to the CNS (including the brain, spinal cord, and leptomeninges) resulting in ischaemia, and less frequently, haemorrhage. PACNS should be distinguished from CNS vasculitis seen in association with a variety of systemic conditions. PACNS is often difficult to diagnose given the lack of specific clinical, imaging, and laboratory characteristics and is associated with significant morbidity and mortality. Clinical presentation is heterogeneous but the most common initial symptoms include acute and subacute focal neurologic deficits, headache, and cognitive impairment/altered cognition. A systematic review found differences in presenting symptoms, neuroimaging results (frequency of cerebral infarction, haemorrhage, and leptomeningeal or parenchymal enhancement), and the predominantly affected vessel type (small vs. medium) between patients. This supports the hypothesis that PACNS lies on a spectrum, with varying histopathologic subtypes (lymphocytic, granulomatous, and necrotizing). Common angiographic findings include segmental stenosis and dilatation (beading), vessel occlusion, collateral circulation, and/or microaneurysms. A distinction should be made between PACNS and its mimics: reversible cerebral vasoconstriction syndrome (RCVS), intracranial atherosclerosis, and secondary vasculitis, especially in angiogram-confirmed cases. Due to the focal and segmental nature of vessel abnormalities, the sensitivity of brain biopsy is often reduced, but remains the only proven way of diagnosing PACNS.

Treatment

- *Induction*: corticosteroids (PO prednisolone 1 mg/kg/day; IV methylprednisolone 1 g/day in severe cases) with cyclophosphamide (monthly IV pulse of 1 g or PO 150 mg/day)
  - Other induction therapies: cyclophosphamide alone or combinations of corticosteroids with azathioprine, mycophenolate mofetil, rituximab, or methotrexate
- *Maintenance*: addition of immunosuppressant with gradual taper of PO corticosteroid
  - Immunosuppressant options: azathioprine (1.5–2 mg/kg/day or 100–200 mg/day), mycophenolate mofetil (2–3 g/day), methotrexate (0.3–0.5 mg/kg/wk or 7.5–20 mg/wk), rituximab (1 g/6mos)

There is no standardized treatment protocol to guide management. Corticosteroids in combination with cyclophosphamide are effective in most patients. Rituximab may be given in treatment-resistant cases. Switching to a safer immunosuppressant, such as azathioprine, methotrexate, or mycophenolate, may be considered after 6 months. Optimal treatment remains unknown.

Evidence base

No RCT evidence exists for any form of treatment of Primary angiitis of the central nervous system (PACNS), and management guidelines represent expert opinion, based primarily on trials investigating therapies for systemic vasculitides with severe organ involvement.[1–5]

Susac's syndrome (SS)

The pathophysiology underlying SS is an autoimmune occlusive microvascular endotheliopathy. Damage to endothelial cells leads to characteristic infarction of target tissues. Anti-endothelial cell antibodies (AECAs) are sometimes found in the serum of patients with SS although it is not known whether AECAs are causative or a result of local endothelial injury. Gass plaques (atheromatous deposits from slow extravasation of blood lipids into the arterial wall at mid-arteriolar segments) are suggestive of SS though are also seen in other disorders, such as Eales disease and lymphoma.

Classically, SS presents with the clinical triad of encephalopathy (headache, cognitive and psychiatric symptoms > cranial neuropathies, seizures), branch retinal artery occlusion (BRAO), and sensorineural hearing loss.[6] However, the full triad rarely manifests at the initial presentation. Other signs can include livedo reticularis and retinal arterio-arterial collaterals. Two clinical subsets are recognized, one with severe neurological involvement, the other with recurrent BRAOs. The neuroimaging triad of SS comprises white matter lesions, deep grey matter lesions, and leptomeningeal disease. Additional diagnostic neuroimaging findings include arteriolar wall hyper-fluorescence (AWH) on fluorescein angiography in retinal arterioles separate from retinal ischaemia, and central callosal lesions on MRI. Treatment depends on the clinical presentation and severity but generally involves early and aggressive immunosuppression.

Treatment

- *First line*: corticosteroids (prednisone orally 80 mg/day with slow taper); if severe, IV methylprednisolone 1 g/day for 3–7 days followed by 80 mg/day prednisone with slow taper; IVIG (initially 2 g/kg over 2 days followed by monthly 0.4 mg/kg for 6 months) with concomitant corticosteroids
- *Second line*: Mycophenolate, rituximab, azathioprine, or cyclophosphamide, intravitreal steroids for ophthalmological presentations
- *Treatment of sequelae*: cochlear implants/hearing aids for hearing loss, hyperbaric oxygen for retinal occlusions

Evidence base

Single case reports and anecdotal evidence support the efficacy of aggressive immunosuppression with corticosteroids. Notably, antiplatelet drugs and anticoagulation are ineffective.[7–9]

Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS)

First described in 2010, CLIPPERS is a chronic CNS inflammatory disorder with an unknown aetiology.[10] Clinically, CLIPPERS is defined by subacute pontocerebellar dysfunction, with or without other CNS symptoms (e.g. cognitive dysfunction, myelopathy), that is responsive to steroids. MRI findings include homogeneous gadolinium-enhancing nodules without ring enhancement or mass effect predominantly in the pons and cerebellum, measuring < 3 mm in diameter, which improve with steroids. Brain biopsy reveals dense lymphocytic (mostly T-cell) inflammation with perivascular predominance and parenchymal diffuse infiltration.

Treatment

- *First line*: Corticosteroids >20 mg/day to achieve relapse-freedom, Methotrexate (10–15 mg/week)
  - Acute relapse: high-dose corticosteroids (IV methylprednisolone 1 g daily for 3–10 days)
- *Second line*: cyclophosphamide, hydroxychloroquine, or azathioprine

Evidence base

No RCT evidence exists for the treatment of CLIPPERS. A few case reports comment on steroid-sparing therapies.[11]

Relapsing polychondritis with neurologic involvement

Relapsing polychondritis (RP) is a rare multisystem disorder targeting cartilaginous and other proteoglycan-rich structures. The underlying pathology remains unknown although it is thought to be driven by both cellular and humoral autoimmunity. Onset of disease is usually in the fifth decade and typical clinical features include auricular and vestibular involvement, arthropathy, nasal chondritis, respiratory tract involvement, cardiovascular disease, ocular, renal, and dermatological abnormalities. Neurological involvement is relatively rare (3–13%) and manifests as encephalitis, aseptic meningitis, or meningoencephalitis.[12]

Treatment

- *First line*: Corticosteroids (prednisolone 0.25–1 mg/kg/day with slow taper).
- *Second line*: Methotrexate, azathioprine, sulfasalazine cyclosporine, cyclophosphamide, infliximab, adalimumab, etanercept, tocilizumab, or abatacept.
- *Symptomatic*: NSAIDs, dapsone, colchicine, indomethacin.

Evidence base

No RCT evidence exists for the treatment of RP. Management is largely based on individual anecdotal reports and translated from data on rheumatoid arthritis.[13] Corticosteroid responsiveness is characteristic but there is a tendency to relapse requiring longer-term immunosuppression.

Multisystem vasculitides with CNS involvement

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) affects ~1 in 1000 of the population. It is more common in African American, Native-American, and Hispanic females. Diagnostic criteria published by the American College of Rheumatology require four of 11 features to be present at some time during the illness: malar rash, discoid rash, photosensitivity, mouth ulcers, arthritis, serositis (pleurisy or pericarditis), renal involvement (casts or proteinuria), neurological disorder, haematological disorder (haemolytic anaemia, cytopenia), immunological disorder, and positive antinuclear antibodies (ANA).

Neuropsychiatric involvement is estimated to occur in between 37 and 95% of patients and includes aseptic meningitis, cerebrovascular disease, demyelinating syndrome (association with anti-aquaporin 4 antibodies), headache, movement disorder, myelopathy, seizures, acute confusional state, anxiety, cognitive dysfunction, mood disorder, psychosis, acute inflammatory demyelinating polyradiculoneuropathy, autonomic disorder, mononeuritis, autonomic disorder, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy. The predominant pathology is a non-inflammatory microangiopathy with cerebral microinfarctions and thrombosis. Macroscopic infarction from Libman–Sacks endocarditis or prothrombotic antibodies can also occur. True inflammatory vasculitis is rare. Cerebral angiography demonstrates segmental stenosis and dilatation in multiple vascular territories. Circulating antibodies include ANA and others directed towards components of cell nuclei.[14–16] Antiphospholipid antibodies, which target β2-glycoprotein, and lupus anticoagulant are prothrombotic and contribute to arterial and venous thrombosis. Antiphospholipid syndrome (APLS) refers to the presence of these prothrombotic antibodies and can occur in association with SLE (or other rheumatological disorders) or in isolation (primary APLS).

Treatment

Non-stroke neurological involvement

Acute

- *First line*: cyclophosphamide (weekly IV pulse or daily PO for 9–12 weeks) plus IV methylprednisolone 1 g/day for 3 days, followed by PO prednisolone 60 mg/day, then taper.
- *Second line*: rituximab, IVIg.

Maintenance

- *First line*: prednisolone (10–20 mg alternate days) plus mycophenolate, azathioprine, or methotrexate.
- *Second line*: rituximab.

Thrombotic complications in antiphospholipid syndrome with or without SLE

Acute

- *First line*: treatment-dose heparin or Low molecular weight heparin (LMWH).

Secondary prevention of thrombotic events

- *First line*: Warfarin
- *Second line*: LMWH

Lifelong anticoagulation with warfarin is the mainstay of therapy for patients with prothrombotic antibodies. Target INR is 2.5– 3.0. In patients with recurrent thrombosis despite warfarin therapy, target International normalised ratio (INR) is increased to 3.0–4.0. Statins can help prevent endothelial cell activation and antimalarial agents are protective against thrombosis in patients with SLE. Low-dose aspirin can be added in patients with cardiovascular risk factors.[17] Pulsed corticosteroids, IVIG, plasmapheresis, and/or eculizumab can be added for catastrophic cases.

Serious (non-stroke) neurological complications of neurological lupus are treated with immunosuppressant therapy, as above. Prednisolone 60 mg daily can be tapered by 10 mg every week to 10 mg daily for 9–12 weeks. Longer-term maintenance is with prednisolone 10–20 mg and either mycophenolate, azathioprine, or methotrexate.

Evidence base

There are no large RCTs for neurological lupus. Treatment of patients with severe neurological involvement is based on one small randomized trial and experience of treating lupus nephritis.[18] Systematic reviews show cyclophosphamide to be superior to pulsed methylprednisolone as a maintenance therapy.[19,20] Small series and case reports suggest that IVIg may be of value. Biological agents are under evaluation. The beneficial effects of rituximab in severe refractory SLE have been reported in 24 case series. Two RCTs failed to achieve their primary endpoints, but both studies were widely acknowledged to have major design limitations.[21] In a double-blind RCT of 86 patients, methotrexate conferred a significant advantage in participants with moderately active lupus by lowering daily prednisone dose by 22% and slightly decreasing lupus disease activity.[22]

Giant cell arteritis

Giant cell arteritis (GCA), or temporal arteritis, is a large-vessel vasculitis, affecting people over the age of 50 years with both cranial and extracranial involvement. Cranial manifestations include headache, scalp tenderness, vision loss, and jaw claudication. Extracranial manifestations include constitutional symptoms, polymyalgia rheumatica, arterial stenoses/aneurysms, and claudication (of the jaw, tongue, or limbs). If untreated, ~40% of patients are at risk of developing permanent visual loss from acute anterior ischaemic optic neuropathy or retinal artery occlusion. Temporal artery biopsy and vascular imaging are key in the diagnosis of GCA. Other clues include an elevated ESR (>60 mm/h), CRP (>2.5 mg/dL), mild anaemia, thrombocytosis, and elevated liver enzymes.

Treatment

Acute

- *First line*:
  - if no visual symptoms—prednisone 1 mg/kg/day up to 80 mg. Tocilizumab co-treatment (USA only)
    - Consider methotrexate
  - if visual symptoms—IV methylprednisolone 500–1000 mg/day for 3–5 days followed by oral prednisolone 1 mg/kg/day up to 80 g. Concomitant tocilizumab (USA only)
    - Consider methotrexate

Maintenance

- *First line*: gradual prednisone taper; aspirin 75 mg daily. Tocilizumab (USA only)
- *Second line*: methotrexate, tocilizumab (Europe), azathioprine, or cyclophosphamide

Evidence base

The advantage of high-dose IV steroids over PO prednisolone is disputed but both significantly reduce the subsequent risk of visual loss.[23,24] A retrospective case series of 15 patients found that all patients responded to monthly pulses of cyclophosphamide, and experienced a corticosteroid-sparing effect, including five patients who discontinued corticosteroids long term, and a literature review of a further 88 patients identified significant treatment response in 84%.[25] In part one of the Giant Cell Arteritis Actemra (GiACTA) trial, a 52-week randomized, double-blind trial, treatment with tocilizumab plus blinded prednisone taper was superior than placebo plus blinded prednisone taper for inducing sustained remission in GCA. Part two of the GiACTA trial, though not randomized, demonstrated sustained remission for at least two years after discontinuation of both tocilizumab and prednisone after a 1-year treatment period in 42% of patients.

Patients who did experience relapses regained remission with the use of tocilizumab.[26] A Cochrane review of tocilizumab in GCA included only two RCTs of 30 and 251 patients, and concluded that tocilizumab may be beneficial in terms of proportion of participants with sustained remission, relapse-free survival, and the need for escape therapy, but recommended more trials. Management differs globally. In USA tocilizumab is licensed as first line in combination with corticosteroids. The Norwegian Society of Rheumatology 2023 recommendations endorse the use of methotrexate in patients with refractory disease or relapse, followed by tocilizumab. The 2020 British Society of Rheumatology Guidelines state that tocilizumab can be considered for GCA, in combination with a glucocorticoid taper, especially in patients at high risk of glucocorticoid toxicity or who relapse, and that TNF inhibitors are not recommended in GCA.

Large retrospective cohort studies support the use of low-dose aspirin for suppressing platelet function and preventing cerebrovascular events. The 2021 American College of Rheumatology/Vasculitis Foundation Guidelines recommend the use of glucocorticoid-sparing immunosuppressive agents.[27] Methotrexate 15–25 mg/week has the best evidence base as a steroid-sparing agent. Large retrospective cohort studies support the use of low-dose aspirin for suppressing platelet function and preventing cerebrovascular events.

Behçet's disease

Behçet's disease (BD) is a chronic relapsing multisystem disorder with mucocutaneous, ocular, vascular, and CNS involvement. Histopathological analysis reveals perivascular infiltration of polymorphonuclear and mononuclear cells. Neuro-BD (NBD) can have both CNS and peripheral nervous system (PNS) manifestations. CNS involvement can be parenchymal or non-parenchymal. Parenchymal involvement presents as brainstem, hemispheric, spinal, and meningoencephalitic syndromes, whereas non-parenchymal disease causes cerebral venous sinus thrombosis and arterial stroke. PNS manifestations include neuropathies, myopathies, and neuromuscular junction disorders. Serum tests supporting the diagnosis of BD include HLA-B51 allele positivity and elevated pro-inflammatory cytokines (TNF-alpha, IFN-gamma, IL-1, IL-6, IL-8). CSF testing may show a high opening pressure, pleocytosis, increased protein, and elevated IL-6.

Treatment

- *First line for an acute attack*: IV methylprednisolone 1 g/day for 5–7 days +/– azathioprine (50 mg/day twice daily up-titrated to a total of 2–3 mg/kg/day) followed by either PO prednisolone (1 mg/kg/day) with a subsequent taper over 2–3 months
- *Second line*: mycophenolate (2–3 g/day) or methotrexate (7.5–25 mg weekly)
- *Third line*: TNF blockers (infliximab, etanercept, adalimumab) or IL6 blockers (tocilizumab)
- *Thrombotic complications*: heparin or LMWH with transition to warfarin (target INR 2.5) or direct-acting oral anticoagulants for 3–6 months

Ciclosporin (typically used in BD uveitis) should be avoided in NBD as it has been linked to an increase in neurologic attacks.

Evidence base

EULAR guidelines recommend prednisolone as described previously.[28] There is no significant evidence base for efficacy of cyclophosphamide, azathioprine, or methotrexate. TNF antagonists and tocilizumab are effective for severe refractory cases.[28–30]

Cerebral venous sinus thrombosis is treated acutely with either IV unfractionated heparin or Subcutaneous low molcular weight heparin (SC LMWH), given together with a short course of glucocorticoids. Direct-acting oral anticoagulants are commonly used as alternatives to warfarin.

Sjögren's syndrome

Rarely CNS involvement occurs in Sjögren's syndrome in the form of transverse myelitis (TM) or NMO, with which there is an overlap (see Chapter 6, Multiple sclerosis and related disorders). More commonly, the PNS is involved (see Chapter 8).

Secondary CNS vasculitis

Secondary CNS vasculitis can occur in the setting of a variety of systemic disorders, including connective tissue diseases, infections (viruses, bacteria, fungi, rickettsia, mycoplasma, and protozoa; infectious endocarditis), systemic vasculitides, autoimmune disorders, and drug use (typically sympathomimetics and drugs of abuse).

IgG4 related disease

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated, chronic multi-organ fibro-inflammatory condition that leads to tumefactive lesions consisting of a lymphoplasmacytic infiltrate with a predominance of IgG4-positive plasma cells, obliterative phlebitis, and storiform fibrosis. More common presentations involve lymph nodes, submandibular and lacrimal glands, pancreas, thyroid, retroperitoneal and cardiovascular systems but IgG4-RD has increasingly been recognized as the underlying pathophysiology in many previously labelled idiopathic neurologic disorders, including orbital inflammation, infundibulo-hypophysitis, hypertrophic pachymeningitis, and rare cases of cranial vascular disease and CNS parenchymal disease.

Treatment

- *First line*: Corticosteroids (intra-orbital or systemic)
- *Second line*: Rituximab
- *Symptomatic*: NSAIDs, dapsone, colchicine, indomethacin

Evidence base

No RCT evidence exists for any form of treatment of IgG4-RD; a retrospective trial showed a response rate of 97% to rituximab.[31]

Neurosarcoidosis

Sarcoidosis is an immune-mediated, multisystem disease characterized by non-necrotizing epithelioid granulomas with scattered lymphocytes, affecting the nervous system in up to 30% of cases. CNS neurosarcoidosis can manifest as meningitis, cranial neuropathy, myelopathy, hypothalamic, or pituitary involvement with endocrinopathy, parenchymal disease, encephalopathy, or neuropsychiatric illness. PNS neurosarcoidosis can include large or small fibre neuropathy and muscle disease. The gold standard for diagnosis remains tissue biopsy.[32]

Treatment

- *First line*: Severe cases 1g IV methylprednisolone or PO bioequivalent pulse dose for 3–5 days followed by PO prednisolone 0.5–1 mg/kg/day; in less severe cases, monotherapy with prednisone 0.25–1 mg/kg/day
- *Second line*: methotrexate (10–25 mg/week with folic acid), azathioprine (2–2.5 mg/kg/day) [hydroxychloroquine, cyclophosphamide (5–10 mg/kg IV monthly for 6–9 infusions), mycophenolate mofetil (500–1500 mg twice a day)]
- *Severe or refractory disease*: TNF inhibitors (infliximab, adalimumab)

Corticosteroids are usually effective, but high doses for prolonged periods are often required. As a rule, up to 20 mg daily is required to maintain symptom freedom, but cautious reduction and withdrawal can be attempted (by 1 mg every 2–4 weeks) if symptoms do not recur. Early initiation of steroid-sparing agents is recommended in patients with moderate-to-severe disease. Rarely, cranial irradiation and neurosurgery may be indicated for hydrocephalus or mass lesions.

Evidence base

Management of neurosarcoidosis has been mainly based on data from pulmonary and systemic sarcoidosis, expert opinion, and observations from case series and reports.[33–35] A few retrospective studies have found the greatest risk of relapse with mycophenolate compared to methotrexate,[36] cyclophosphamide, and infliximab. Case reports and small series have suggested efficacy of infliximab for NS. A multi-institutional study in 2017 reported benefit with infliximab for CNS sarcoidosis with 77% responding clinically (29% of whom achieved complete remission). Positive outcomes with infliximab were reported in other series, including 87% with clinical stability or improvement in a series from Utah and clinical stability or improvement in 96% (remission in 21%, improvement in 50%, and stability in 25%) in a series from the Netherlands.[37] Investigations are underway regarding the utility and safety of Janus kinase (JAK) inhibitors (tofacitinib, baricitinib) and tocilizumab.

Autoimmune encephalitis

Autoimmune encephalitis encompasses a group of immune-mediated, non-infectious inflammatory conditions affecting the brain. The immune reaction is usually diffuse and can involve the meninges, spinal cord, and/or the PNS. Accurate diagnosis of autoimmune encephalitis requires careful clinical phenotyping supported by antibody testing and other ancillary investigations, and is aided by the following diagnostic criteria: (1) subacute onset (rapid progression <3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms; (2) at least one of the following: new focal CNS findings, seizures not explained by a prior seizure disorder, CSF pleocytosis (WBC >5 cells/mm^2), MRI features suggestive of encephalitis; (3) reasonable exclusion of alternative causes.

In recent years, antibodies directed against cell surface antigens have been detected in cases of non-infectious limbic encephalitis. Different clinical phenotypes are associated with specific autoantibodies as follows.[38,39]

- *AMPAR antibody encephalitis* presents as a rapidly progressive encephalitis, often with acute psychosis. Thymoma, small cell lung cancer (SCLC), or breast cancer are present in 70% of cases.
- *GABABR antibody encephalitis* is characterized by prominent temporal lobe seizures in the setting of a subacute encephalopathy. Half of cases are associated with SCLC.
- *GABAAR antibody encephalitis* is associated with a rapidly progressive encephalopathy with seizures or status epilepticus.
- *GlyR antibody encephalitis* presents with progressive encephalomyelopathy with rigidity and myoclonus (PERM) or stiff-person spectrum disorder. Thymomas, Small cell lung cancer (SCLC), and leukaemias have been associated with the syndrome.
- *NMDAR antibody encephalitis* is pathogenically associated with CSF IgG antibodies against the GluN1 subunit of the N-methyl-D-aspartate (NMDA) receptor and typically shows a 4:1 predilection for females:males. Subacute cognitive and behavioural change, psychosis, and seizures are followed by choreoathetosis and dysautonomia, then mutism and catatonia. Ovarian teratoma is present in up to 50% of cases.
- *Bickerstaff's brainstem encephalitis* can be associated with IgG anti-GQ1b antibodies (as in Miller-Fisher syndrome) and is characterized by subacute onset of impaired consciousness, ataxia, and bilateral ophthalmoparesis, preceded by an infectious event.
- *LGI1 antibody encephalitis* more commonly affects males and presents with faciobrachial dystonic seizures. Hyponatraemia can also be seen.
- *CASPR2 antibody encephalitis* is most commonly seen in males and is characterized by Morvan syndrome and neuromyotonia. Fifteen percent of cases are associated with a thymoma.
- *DPPX antibody encephalitis* is associated with a rapidly progressive encephalopathy and often, prodromal diarrhoea.
- *Neurexin 3alpha antibody encephalitis* has a prodrome of fever, headache, and gastrointestinal symptoms, followed by confusion, seizures, and depressed consciousness. There is a female predominance.
- *IgLON5 antibody encephalitis* primarily affects adults and symptoms include non-REM parasomnia with stridor, bulbar dysfunction, and gait instability.
- *mGluR5 antibody encephalitis* can be associated with Hodgkin's lymphoma and typically presents with subacute memory loss and psychosis.
- *mGluR1,2 antibody encephalitis* Subacute cerebellar ataxia is usually the clinical presentation and there is an association with Hodgkin's lymphoma, adenocarcinoma, and rhabdomyosarcoma.
- Anti-Glutamic acid decarboxylase (*Anti-GAD*) *encephalitis* typically affects younger people; seizures are prominent, and there may be associated stiff-person and cerebellar syndromes. PERM is another very rare clinical manifestation of GAD and/or glycine-mediated encephalopathy. It should be noted that GAD is not a surface antigen.

Treatment

- *First line*: 1 g IV methylprednisolone for 3–7 days plus IVIg (2 g/kg over 2–5 days) or PLEX (5–10 sessions every other day)
- *Second line*: rituximab, cyclophosphamide, azathioprine.

Empiric antibiotics and antivirals are always recommended prior to definitive exclusion of an infectious cause.

Removal of underlying tumours, notably ovarian teratoma in NMDAR encephalitis, can expedite and help to maintain recovery.

Evidence base

Evidence suggests that early and aggressive immunotherapy improves outcomes.[40,41] A few case series have shown responses to bortezomib and tocilizumab. A placebo-controlled clinical trial of IVIg is currently underway but otherwise there are no RCTs of immunotherapy in autoimmune encephalitis, and treatment, particularly relating to the choice of second- and third-line treatments, is guided by expert consensus, depends on the syndrome, severity, and scenario and is based on experience with other antibody-mediated neurological disorders.[42]

Paraneoplastic neurologic syndromes

Paraneoplastic neurologic syndromes are caused by an immune-mediated remote effect of cancer and should be distinguished from brain metastases, leptomeningeal carcinomatosis, cancer-associated coagulopathy, treatment-related neurotoxicity, metabolic syndromes, or infections. Pathogenesis is thought to involve an immune cross-reaction between tumour and neural antibodies. Neurologic phenotypes have been described as follows.

- *Encephalomyelitis*; anti-Hu (ANNA-1) and CV2 (CRMP5) antibodies are found in association with SCLC.
- *Anti-NMDAR encephalitis*—associated with ovarian teratoma.
- *Limbic encephalitis* presents with subacute memory loss, seizures, and psychiatric symptoms over a period of less than 3 months. The autoimmune antibodies, GABABR and AMPAR, can be seen in the paraneoplastic form, though anti-Hu and anti-Ma2 antibodies are more common.
- *Rapidly progressive cerebellar syndrome* typically affects gait and is associated with anti-Yo and Delta and Notch-like epidermal growth factor—related (DNER) antibodies. Cerebellar atrophy may not be present at onset of disease.
- *Opsoclonus-myoclonus syndrome (OMS)* is characterized by involuntary, high-frequency, chaotic multi-directional eye movements, and non-rhythmic action myoclonus. Other features include cerebellar involvement and encephalopathy. OMS is classically seen in children with neuroblastoma or in adults with SCLC or breast cancer. Anti-Ri (ANNA-2) antibodies are common.
- *Sensory neuronopathy* typically affects sensory neurons of the dorsal root ganglia. Frequently associated antibodies are Hu, CV2 (CRMP5), and amphiphysin.
- *Gastrointestinal pseudo-obstruction* is due to myenteric plexus dysfunction and presents with recurrent abdominal pain, distension, constipation, and/or vomiting., Hu antibodies can be seen.

- *Lambert-Eaton myasthenic syndrome* presents with progressive proximal muscle weakness followed by autonomic dysfunction. Improvement is classically seen with repeat exercise or maximal voluntary contraction. Nearly 90% of patients have antibodies against P/Q type voltage-gated calcium channels (VGCCs). Patients with underlying SCLC often have anti-glial nuclear (SOX1) antibodies.

Less common phenotypes: brainstem encephalitis (Ma2 antibodies with testicular tumours or non-SCLC), Morvan syndrome (malignant thymoma; CASPR2 antibodies), isolated myelopathy (breast and lung carcinomas; CV2 and amphiphysin antibodies), stiff-person syndrome (amphiphysin antibodies and breast cancer), and polyradiculoneuropathies (CV2, amphiphysin, PCA-2 antibodies; SCLC and breast cancer)

Treatment

- *First line*: high-dose corticosteroids, IVIG, and PLEX (administered individually or in combination).
- *Second line*: cyclophosphamide, rituximab.
- *Third line (based on case reports only)*: natalizumab and tacrolimus (anti-Yo or Hu antibodies), bortezomib, tocilizumab, intrathecal methotrexate (antibodies against cell surface antigens).

Treatment of the underlying malignancy is essential. When no particular tumour is suspected, a full-body CT followed, if negative, by fluorodeoxyglucose-PET/CT is warranted, and regular follow-up screening is recommended if a tumour is still not identified. Cancer identification can be difficult especially if PNS is the first symptom. Antibody-guided cancer screening can be helpful (i.e. SCLC in patients with Hu antibodies). Evidence exists that specific PNS (especially those associated with Ma2 and Hu antibodies) can be triggered by cancer immunotherapy. Treatment with an immune checkpoint inhibitor should be halted if PNS develops.

Evidence base

There are no RCTs of immunotherapy in PNS and treatment is based on expert consensus, case series/reports and multidisciplinary opinion. First-line +/– second-line therapies may be helpful but treatment of the underlying cancer is most crucial.[43]

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Chapter 8

Disorders of peripheral nerves

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Introduction

The commonest disorders of the peripheral nerves encountered in clinical practice are the chronic length-dependent axonal polyneuropathies seen in association with diabetes mellitus, alcohol overuse, and, worldwide, leprosy (see Table 8.1 for a comprehensive list) as well as the entrapment mononeuropathies. Chronic neuropathies are classified as primarily demyelinating or axonal, on the basis of electrodiagnostic and/or pathological criteria. Management of chronic axonal neuropathies generally involves treatment of the underlying cause, which may result in stabilization

Table 8.1 Causes of polyneuropathies

Chronic axonal polyneuropathy	Chronic demyelinating polyneuropathies	Acute polyneuropathies
Diabetes mellitus Alcohol Uraemia Cirrhosis Amyloidosis (associated with plasma cell dyscrasia/ myeloma) Hypothyroidism Acromegaly Toxins (acrylamide, arsenic, lead, mercury, thallium, organophosphates, carbon disulfide, organic solvents) Drugs (see Chapter 21, Drugs causing neurological disease) Deficiency syndromes—primarily B vitamins Paraneoplastic Hereditary—Charcot–Marie–Tooth disease type 2 (CMT2), amyloidosis, Fabry, porphyria, Refsum Infection—leprosy, HIV Idiopathic Rare—Sjögren's syndrome, vasculitis, sarcoidosis	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) Multifocal motor neuropathy with conduction block (MMN) Paraproteinaemic neuropathy Hereditary polyneuropathies	Guillain–Barré syndrome (GBS) Rabies and post-rabies vaccine Diphtheria Heavy metals, industrial toxins Drugs (see Chapter 21, Drugs causing neurological disease) Acute intermittent porphyria Vasculitic neuropathy Critical illness neuropathy Thiamine deficiency Lymphomatous neuropathy

or resolution of the neuropathy (e.g. optimal diabetes control, abstinence from alcohol, withdrawal of causative medication). Demyelinating neuropathies are further classified as hereditary or acquired, the acquired neuropathies being immune-mediated and thus amenable to treatment. Their management is the focus of much of this chapter. The management of vasculitic neuropathy and Bell's palsy are also included in this chapter.

Acute inflammatory demyelinating polyradiculoneuropathy/Guillain–Barré syndrome

Guillain-Barre syndrome (GBS), is the most frequent cause of acute or subacute neuromuscular paralysis worldwide.[1] Acute inflammatory demyelinating polyradiculopathy (AIDP) is the most common subtype of GBS. Two-thirds of cases are preceded by an upper respiratory or gastrointestinal infection, the most commonly identified being *Campylobacter jejuni* gastroenteritis. Other less common triggers include surgery, pregnancy, cancer, and vaccination. The usual presentation is of a few days' history of sensory symptoms, followed by a progressively ascending flaccid weakness and areflexia, often with back pain, cranial nerve involvement, and autonomic dysfunction. The nadir is usually reached within 2 weeks and by definition at a maximum of 4 weeks. Up to 30% of patients require intubation and ventilation due to respiratory failure.

The CSF is usually acellular, with an elevated protein level. Nerve conduction studies may be normal in early AIDP or show proximal block in the form of prolonged F waves. In established AIDP, small action potentials, prolonged distal motor latency (DML), delayed F waves, and conduction block are seen. Sural sparing is a common phenomenon when testing sensory nerves. Antiganglioside antibodies (mostly anti-GM1) are detected in 25%. MRI may show post-gadolinium enhancement of lumbar roots.

Most cases are monophasic, and only 3% ever relapse. A slow recovery over weeks or months is the rule, and 80% of patients regain the ability to walk independently at 1 year. The mortality rate remains 5%, and poor prognostic factors include late age at onset, preceding diarrhoea, or C. *jejuni* infection, need for intubation and ventilation within the first week, and severe weakness. Only a very small proportion of patients go on to develop a relapsing disease course, requiring a retrospective revision of the original diagnosis to CIDP.

GBS variants

Rare subtypes include purely axonal forms, such as acute motor axonal neuropathy (AMAN), often associated with anti-GD1a and GM1 immunoglobulin G (IgG), and acute mixed sensory and motor neuropathy (AMSAN). The rare Miller Fisher variant presents with the triad of ophthalmoplegia, areflexia, and sensory ataxia. Anti-GQ1b antibodies are present in over 95% of cases of Miller Fisher syndrome. Several focal 'forme fruste' GBS variants are also described, including the pharyngeal-cervical-brachial presentation.

Treatment of AIDP

Supportive care

- Monitoring: vital capacity, cardiac rhythm, and BP.
- Venous thromboemboism (VTE) prophylaxis: thromboembolic deterrent stockings or SC heparin as per local guidelines.
- Pressure area prophylaxis with specialized bed and/or frequent turning.
- Management of constipation and dysphagia.
- Analgesia for neuropathic pain: (see Neuropathic pain, Chapter 5). Opioids are recommended for short-term use only.

Disease-modifying treatment

- Plasma exchange (PLEX), five plasma volumes over 1–2 weeks, or IVIg 0.4 g/kg/day for 5 days.[2]
- Corticosteroids are not of benefit.
- All patients who are not ambulant within 2 weeks of onset should receive IVIg (0.4 g/kg/day for 5 days) or PLEX (five plasma volumes over 1–2 weeks). Both treatments hasten recovery, but IVIg is often preferred due to ease of administration. Many clinicians would give IVIg to ambulant, but disabled, patients, particularly in the early stages when there is continuing disease progression.
- Early physical and occupational therapy are recommended to maintain range of motion, prevent contractures, and begin the rehabilitation process.

Evidence base

Several large RCTs have demonstrated superiority of PLEX over supportive care alone in terms of improving median time to walking with aid.[3] It is of greatest benefit if instituted within 7 days, and four exchanges have been shown to be superior to two. Head-to-head trials have shown equivalence of IVIg to PLEX in hastening recovery.[5,4] Combining the two treatments does not confer additional benefit. In patients who do not benefit from one course of treatment, a further course of the same modality can be considered. The choice between PLEX and IVIg is guided by local availability and patient co-morbid factors (see Table 8.2). There is no evidence that corticosteroids or any other immunomodulatory treatments are of benefit in GBS.[5]

Table 8.2 Acute treatment of GBS—PLEX vs. IVIg

Modality	PLEX	IVIg
Advantages	Can be used in significant renal impairment and true IgA deficiency	More likely to complete course of treatment Easier to administer
Disadvantages	Relative contraindication in patients with haemodynamic instability. Often impractical	Costly
Complications	Sepsis, hypotension, vascular access difficulties	Aseptic meningitis, acute renal failure

Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the commonest acquired cause of chronic demyelinating neuropathy.[7] It occurs with a prevalence of 1–9 per 100 000 and is more common in older males. It is immune-mediated and antibodies to the nodal and para-nodal antigens neurofascin 155, neurofascin 140/186, and contactin-1 have been found in roughly 15% of affected patients. CIDP resembles GBS clinically but has a more protracted course progressing over months to years. A history of preceding infection is not generally seen. CIDP is recognized as a syndrome with both 'typical' and 'atypical' variants. Typical CIDP commonly presents with symmetric proximal and distal weakness and sensory dysfunction in all extremities; atypical CIDP is also characterized by motor and/or sensory peripheral nerve involvement but the pattern of involvement or modality predominantly affected can vary. Regardless of the typical or atypical nature, symptoms evolve over two months in a step-wise (relapsing remitting) or progressive course. Other symptoms include fatigue, pain, tremor, mild autonomic dysfunction, and cranial nerve involvement. CSF protein is elevated in the presence of a normal CSF white cell count (WCC). Neurophysiology shows slowing of nerve conduction or partial conduction block with prolongation of DMLs and prolonged or absent F waves, consistent with demyelination.

CIDP variants

Whether CIDP is a disease or a syndrome remains controversial.[6] A number of atypical variants exist, including motor and sensory predominant forms, MADSAM/Lewis–Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy) and CIDP with CNS involvement. CIDP is also seen in association with a variety of systemic disorders, including diabetes mellitus, paraproteinaemia (see paraproteinaemic neuropathy section), plasma cell dyscrasias, HIV infection, chronic hepatitis B or C, SLE, connective tissue diseases, sarcoidosis, Lyme disease, inflammatory bowel disease, lymphoma, nephrotic syndrome, organ and bone marrow transplants, and thyrotoxicosis.

Treatment of CIDP

- *First line*: periodic IVIg (2 g/kg over 2–5 days), twice-weekly PLEX (4–6 exchanges over 8–10 days), or oral prednisone.
- *Second line*: azathioprine (2 mg/kg/day, starting at 50 mg od and increasing weekly by 50 mg), methotrexate (15 mg weekly), or interferon-beta-1a.

Evidence base

A Cochrane review of treatment for CIDP was recently published8: corticosteroids have uncertain value (very low evidence) though are commonly used due to their low cost and widespread availability, PLEX has moderate-quality evidence, and Intravenous immunoglobulin (IVIG) has the highest-quality evidence. Second-line options showed low-moderate-quality evidence.

There is currently no consensus on the optimum corticosteroid dosing regimen or route of administration. IVIg improves disability in CIDP for 2–6 weeks.[9] Due to the short-lived effects of IVIg, up to 85% of patients will require maintenance dosing at intervals of 2–6 weeks; at this point, doses may be tapered to 1 g/kg over 1–2 days. PLEX is effective for short-term treatment of CIDP.[10] Cross-over trials have shown no difference in short-term efficacy between IVIg and PLEX, or between IVIg and corticosteroids. Choice of first-line therapy is guided by disease severity, treatment availability, side effects, co-morbidities, and cost. For severe disease, initial therapy with IVIg or PLEX, rather than corticosteroids, is recommended. Corticosteroids may be more suitable for patients with slower-onset CIDP. There are no robust RCT data available to guide choice of any particular second-line immunomodulatory therapy[11] and current data do not demonstrate significant benefit from any of these treatments.

Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a very slowly progressive, pure motor syndrome, causing asymmetric weakness, wasting, and fasciculation, predominantly in the upper limbs.[12] Serum IgM anti-ganglioside antibodies (anti-GM1) are present in the majority of patients and these antibodies cause sodium and potassium channel dysfunction at or around the node of Ranvier of myelinated motor axons, leading to the characteristic motor conduction block (with sparing of sensory nerves) seen on neurophysiological testing. CSF protein levels are typically normal. Multifocal motor neuropathy has been associated with tumour necrosis factor alpha blockers, including infliximab.

Treatment of MMN

- *First line*: periodic IVIg (initial dose of 0.4 g/kg/day for five consecutive days (total of 2 g/kg); maintenance doses range from 0.4 g/kg once weekly to 2 g/kg every 8 weeks) or subcutaneous IG (SCIG) at the same dose.
- *Second line*: rituximab or cyclophosphamide for resistant cases.

More than 80% of patients respond to IVIg and roughly 20% achieve long-term remission. Corticosteroids make MMN worse, and paradoxically PLEX is ineffective.[13]

Evidence base

An open-label study of 44 adults with MMN randomized 1:1 to either double-blind treatment of IVIg followed by placebo for 12 weeks each, or the reverse, confirmed significant benefit of IVIg, compared to placebo.[14] Mean maximal grip strength declined 31.38% during placebo and increased 3.75% during IVIg ($p = 0.005$). In 35.7% of participants, Guy's Neurological Disability scores for upper limbs worsened during placebo, and not during IVIg, treatment, whereas the converse was true in 11.9% ($p = 0.021$). Sixty-nine per cent deteriorated and switched prematurely from placebo to open-label IVIg, and 2.4% switched from blinded to open-label IVIg ($p <0.001$). Clinical investigations have shown that SCIG is a safe, equally effective, feasible alternative to IVIG that can be administered in the home.

There are no RCTs of immunosuppressive agents. Cyclophosphamide and rituximab have led to some benefit in case reports of refractory cases.

Paraproteinaemic neuropathies

Paraproteinaemic neuropathies (PPN) are a heterogeneous set of neuropathies characterized by the presence of monoclonal immunoglobulin (M-protein) in the serum. There are three major clinical subtypes of PPN: distal demyelinating symmetric neuropathy (associated with IgM +/– MAG), CIDP-like (associated with IgG and IgA), and length-dependent axonal sensorimotor polyneuropathy, often with allodynia, hyperpathia, cramps, or mild distal weakness.

Peripheral neuropathy symptoms may precede by years the emergence of paraproteinaemia, whether it be haematologic malignancy (multiple myeloma, cryoglobulinemia, lymphoma, amyloidosis, Waldenstrom macroglobulinemia) or monoclonal gammopathy of undetermined significance (MGUS).

Therapies depend on the particular PPN subtype and range from immunotherapies to rituximab and various chemotherapies.[15,16] Associations between MGUS, particularly IgA and IgG, and indolent neuropathies may be coincidental and often treatment is not required. CIDP-like presentations are treated in the same way as CIDP.[16] IgM PPN with or without anti-MAG, and POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein spike, and skin manifestations) are well-characterized syndromes with specific treatment options as outlined next. Another rare but distinct variant is CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies).

IgM paraproteinaemic neuropathy +/– anti-MAG

This presents as 'distal acquired demyelinating symmetric' (DADS) sensory and motor neuropathy. It is usually very slowly progressive, predominantly distal with sensory ataxia, little or no weakness, and frequent tremor. There is often a benign course with little functional deterioration over time; however, the neuropathy may evolve more rapidly at certain stages. One study found that 10 and 15 years after onset, 24% and 50% of patients were disabled, respectively. In more than 75%, the monoclonal IgM recognizes myelin-associated glycoprotein (MAG) and other peripheral nerve glycolipids.

Treatment of IgM anti-MAG neuropathy

Treatment, when indicated, is guided by M-protein levels and clinical severity of the neuropathy. Rituximab is first line treatment, given off-label. Corticosteroid monotherapy is not effective, but corticosteroids benefit ~50% patients when given in combination with other therapies. IVIg and PLEX are of limited and short-term benefit only. Second-line agents include fludarabine, chlorambucil or cyclophosphamide, or a combination of immunotherapy and chemotherapy.[17]

Evidence base

Open-label studies and two RCTs indicate that rituximab is the best agent available, providing long-term benefits to almost 50% of treated patients.[18,19] A retrospective study of 45 patients given rituximab alone or in combination with either fludarabine or cyclophosphamide found that 80% of patients responded to immunotherapy or immunochemotherapy, but that combination therapy produced a more rapid clinical response.[20,21]

POEMS syndrome

POEMS syndrome (*P*olyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal protein, *S*kin changes) is a rare condition characterized by the presence of a monoclonal plasma cell disorder and peripheral neuropathy, along with other systemic symptoms (nail clubbing, hyperpigmentation, ascites, elevated serum vascular endothelial growth factor (VEGF) levels, Castleman's disease, and osteosclerotic bone lesions/myeloma). The neuropathy usually presents with positive sensory symptoms and slowly progressive distal weakness. If untreated, POEMS syndrome has a poor prognosis with a median survival of 12–33 months. Treatment is based on that used for multiple myeloma and includes radiotherapy to bony lesions, and excision of solitary bony lesions. The most commonly used systemic therapies for POEMS syndrome include alkylators and steroids, high-dose chemotherapy with autologous stem cell transplantation, lenalidomide, and bortezomib. Outcomes can be excellent if the diagnosis is made early and appropriate therapy is used.[22]

Vasculitic neuropathy

Vasculitis can affect the vasa nervorum of peripheral nerves, causing critical ischaemia of the nerves. Causes include primary systemic vasculitis, vasculitis secondary to other conditions such as connective tissue disorders (rheumatoid arthritis, SLE), infectious, paraneoplastic, and drug-induced conditions, and isolated or non-systemic vasculitic neuropathy. Pathogenesis varies, depending on the underlying condition, but may involve immune complex deposition within vessel walls, prominent in cryoglobulinaemia and polyarteritis nodosa (PAN), and/or T-cell-mediated immune mechanisms as seen in ANCA-associated disease. Three patterns of nerve involvement are seen in vasculitic neuropathy: mononeuritis multiplex, distal polyneuropathy, and radiculoplexopathy. Onset may be abrupt or insidious; both motor and sensory nerves can be involved, and pain may be prominent.

When vasculitic neuropathy is associated with an identifiable systemic vasculitis or connective tissue disease, immunosuppressive therapy is directed at the underlying disease.

Primary systemic vasculitides with peripheral nerve involvement

Systemic vasculitides commonly affecting the peripheral nerves include ANCA-associated vasculitis, PAN, and mixed cryoglobulinaemia. When vasculitic neuropathy is associated with an identifiable systemic vasculitis or connective tissue disease, immunosuppressive therapy is directed at the underlying disease.

ANCA-associated vasculitic neuropathies

The ANCA-associated vasculitides comprise three distinct conditions: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg-Strauss syndrome). They most commonly present with mononeuritis multiplex. To induce remission, glucocorticoids combined with cyclophosphamide, rituximab, methotrexate, or mycophenolate mofetil is considered, depending on the severity of the condition. For maintenance of remission, a combination of low-dose glucocorticoids and azathioprine, rituximab, methotrexate, or mycophenolate mofetil may be used. The efficacy of anti-interleukin-5 therapy (i.e. mepolizumab) has been demonstrated in the case of refractory or relapsing EGPA. Several other new agents, including avacopan, vilobelimab, and abatacept, are under development.[23]

Polyarteritis nodosa-associated neuropathy

PAN is a systemic necrotizing vasculitis involving medium and small-sized muscular arteries with multisystem manifestations. Peripheral nerve involvement can occur in PAN, and usually presents as a subacute or chronic mononeuritis multiplex or a confluent neuropathy. Treatment is generally immunosuppression with glucocorticoids plus cyclophosphamide, or biologic agents (e.g. TNF inhibitors, interleukin 6 inhibitor).[24] Hepatitis B-associated PAN is treated with antiviral therapy and PLEX.[25]

Cryoglobulinaemic neuropathy

Cryoglobulins are antibodies that precipitate at low temperatures and dissolve after rewarming. Cryoglobulinaemia usually presents with a systemic inflammatory syndrome with fatigue, arthralgia, purpura, ulcers and typically a selective small fibre sensory neuropathy due to deposition of circulating cryoglobulins in the vasa nervorum. Cryoglobulinaemia is most often associated with chronic hepatitis C infection, but other infections (hepatitis B, EBV, HIV), lymphoproliferative malignancies, and autoimmune diseases (SLE, Sjögren’s) may also be responsible.

Treatment depends on the cause of cryoglobulinemia. For patients with chronic hepatitis C infection, antiviral therapy is indicated. Immunosuppressive or immunomodulatory therapy, including steroids, plasmapheresis, and cytotoxic agents, is reserved for organ-threatening manifestations.[26]

Isolated (non-systemic) vasculitic neuropathy

Treatment

Mild disease

- *Induction*: prednisolone 1 mg/kg/day for 4 weeks, tapering over at least 6 months[1]*

Moderate to severe disease (rapidly progressive or resistant to first-line treatment)

- *Induction*: IV methylprednisolone 1 g daily for 3 days, followed by prednisolone 1 mg/kg/day for 4 weeks (taper over at least 6 months[2]*)
- Combination with cyclophosphamide PO 2 mg/kg daily or IV pulses 750 mg/m^2 body surface area (BSA)[3]** every 4 weeks (plus mesna and trimethoprim–sulfamethoxazole) for 6 months.

Maintenance: azathioprine (1.5–3 mg/kg/day) or methotrexate (initially 15 mg/week) for 18–24 months, discontinuing after 6–12 months' disease-free period.

Evidence base

There are no adequate RCTs on which to base treatment for non-systemic vasculitic neuropathy. Therefore, therapeutic decisions are based primarily on clinical experience, observational data, and extrapolation from trials of immunosuppressive agents used for primary small to medium vessel systemic vasculitides.[27]

Bell's palsy

Bell's palsy is an acute peripheral facial nerve palsy of unknown cause, which, in most cases, is probably due to herpes simplex virus (HSV) reactivation. It accounts for at least half of all cases of peripheral facial palsy, with an annual incidence of 13–34 per 100 000; the risk is increased during pregnancy. Presentation is with sudden-onset unilateral facial paralysis. Hyperacusis and ipsilateral taste disturbance may be present, and rarely ipsilateral facial sensory loss occurs.

Treatment

- *First line*: prednisolone 50–80 mg/day for 7–10 days.
- *Second line*: consider aciclovir 800 mg tds or valaciclovir 1000 mg tds for severe facial palsy.

The mainstay of treatment for Bell's palsy is early oral corticosteroid therapy, ideally beginning within 3 days of onset of symptoms. There is no consensus regarding the optimum regimen for corticosteroid therapy, and practice varies, but 7–10 days of treatment is generally given. The use of concomitant antiviral therapy with aciclovir for confirmed Bell's

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1,2 * Suggested regime. Reduce by 10 mg each week to 40 mg/day, then by 5 mg each week to 20 mg/day, then by 2.5 mg each week to 10 mg/day, then by 1 mg every 2 weeks to 5 mg/day. Further taper by 1 mg every 2 weeks if stable disease.

3 ** Cyclophosphamide IV pulse should be reduced to 500 mg/m^2 BSA if obese, age >70 years, renal impairment, or neutropenia <1.5.

palsy is recommended for severe cases only. The presence of vesicles in the external auditory meatus, however, suggests varicella-zoster reactivation (Ramsay Hunt syndrome), rather than Bell's palsy, and warrants early treatment with an antiviral agent. It is also important to protect the ocular surface from the effects of poor eyelid closure. Regular lubricating eye drops, taped eyelid closure, and sutures may be required in some cases. Ophthalmology review can often be helpful.

Evidence base

There is good-quality evidence of the efficacy of prednisolone in the treatment of Bell's palsy. Prednisolone treatment was shown to reduce the risk of an unfavourable outcome from Bell's palsy by 31% in a large meta-analysis of 2786 patients.[28] Treatment with antiviral agents alone does not significantly improve recovery. A randomized prospective study showed additional benefit of antiviral therapy for acute severe Bell's palsy but a 2019 Cochrane database review of 14 RCTs, including 2488 patients did not find robust supportive evidence for co-treatment of all cases.[29,30] There is limited evidence regarding the use of electrical nerve stimulation to promote motor recovery. Although case reports and small case series have suggested some benefit, there have been no controlled trials, and it is not currently recommended.

Sjögren's syndrome

Sjögren syndrome (SS) is a chronic, systemic, autoimmune disorder characterized by lymphocytic infiltration of the exocrine organs (lacrimal and salivary glands), leading to sicca symptoms and parotid enlargement. It can occur in a primary form or as a complication of other autoimmune diseases (most commonly rheumatoid arthritis). Diagnosis of SS requires the satisfaction of four of six internationally defined criteria: symptoms of dry eyes, positive Schirmer's, or Rose Bengal dye test, symptoms of dry mouth, focal lymphocytic sialoadenitis on minor salivary gland biopsy, demonstration of either reduced salivary flow on scintigraphy or diffuse sialectasia on parotid sialography, and serum autoantibodies to Ro (SSA) or La (SSB).

Neurological involvement occurs in approximately 20% of cases. Neurological symptoms may precede the characteristic sicca symptoms, and anti-Ro and La antibodies are often absent, making the diagnosis challenging. The most prevalent neurological manifestation is peripheral neuropathy, which occurs in 15% of cases. The commonest type is distal axonal polyneuropathy (PN) (80% of patients with PN) which may be purely sensory or sensorimotor. Sensory neuronopathies/ganglionopathies comprise the majority of other PN cases. Myelopathies and peripheral and cranial mononeuropathies, particularly trigeminal, are also occasionally described.[31]

Treatment of SS peripheral neuropathy

Immunosuppression is generally necessary for neurological involvement and may include corticosteroids, IVIg, azathioprine, cyclophosphamide, PLEX, infliximab, or rituximab.

Evidence base

There is a lack of high-quality randomized trial data regarding the treatment of neuropathy in Sjögren's syndrome. Glucocorticoid therapy is the most tested intervention with conflicting results.[31] Oral prednisolone 0.5–1 mg/kg/day or pulsed methylprednisolone appear to be of more benefit when vasculitis is present. In one prospective cohort study prednisolone in combination with cyclophosphamide or IVIg in patients with pure sensory neuropathy, resulted in a clinical stabilization or improvement in most cases for a mean follow-up period of 10 years. In contrast, a retrospective cohort study found no beneficial effect of steroids in patients with axonal polyneuropathy or ganglionopathy.

IVIg studies have shown promising results. Doses of 2 g/kg over 2–5 days as a single course or repeated every month resulted in improvement in two studies of patients with non-vasculitic PN, with more benefit seen in those with painful sensory neuropathies rather than ganglionopathies.

Small case series suggested that some benefit from combining cyclophosphamide or mycophenolate with corticosteroids. A recent study of IVIg in SS patients with painful pure small fibre neuropathy reported significant improvement in pain allowing discontinuation of analgesia in 75% and reduction in analgesia dose in all of 12 patients following IVIg treatment, sustained for at least 25 months.[32]

Sarcoidosis

Sarcoidosis affects the CNS, the PNS, or both. Cranial neuropathies are the commonest manifestation of neurosarcoidosis. Other peripheral manifestations include myopathy and, rarely, peripheral polyneuropathy (refer to Chapter 6, Multiple sclerosis and related disorders, for management of neurosarcoidosis)

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Chapter 9

Motor neuron disease

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Introduction

Motor neuron disease (MND) encompasses a group of conditions characterized by progressive loss of motor neurons.[1] Clinical features are determined by the relative involvement of upper and lower motor neurons (UMN and LMN), and typically include weakness, in combination with LMN signs of wasting and fasciculation, and/or UMN signs such as increased tone, hyperreflexia, and upgoing plantar responses. Neuropsychiatric syndromes, most commonly emotional lability, frontotemporal cognitive impairment, and dementia are relatively common. The prognosis is typically poor, with an average survival of 2–3 years from diagnosis, although there is considerable variation between individuals and MND subtypes. Up to 20% of patients survive beyond 5 years, and a small percentage are alive 10 years after diagnosis.[1,2]

MND is usually subdivided based on the degree of UMN and LMN involvement.

- Amyotrophic lateral sclerosis (ALS)—mixed UMN and LMN involvement
- Primary lateral sclerosis (PLS)—isolated UMN involvement
- Progressive muscular atrophy (PMA)—isolated LMN involvement

ALS is predominantly considered a sporadic condition, but over 10% of cases are familial, with several genes now causally linked to the disease.[1]

The broader spectrum of MND also includes defined genetic disorders of spinal muscular atrophy (SMA), hereditary spastic paraplegia (HSP), and spinal and bulbar muscular atrophy (SBMA, Kennedy's disease).[2] These often have an identifiable genetic cause, and adult-onset cases generally exhibit much slower progression than ALS. See Neurogenetics, Chapter 22 p. 303, for more details on the genetic causes of ALS and SMA.

Amyotrophic lateral sclerosis

ALS is the commonest form of MND, accounting for around 70% of cases.[1] Onset is usually in the seventh decade of life. The clinical hallmark is mixed UMN and LMN features in the limbs, trunk, and/or bulbar musculature with the classic combination of weakness, fasciculations, and wasting, brisk reflexes, and extensor plantar responses. The area of involvement at presentation varies.[2] About one-third of patients present with upper limb symptoms, one-third with lower limb symptoms, slightly fewer than one-third with bulbar dysfunction, and 1–2% with isolated respiratory failure. Clinically significant frontotemporal dementia occurs in up to 15%, but half of all patients have a degree of cognitive impairment.[1] Widespread denervation and reinnervation on neurophysiology are helpful to confirm the clinical diagnosis. Respiratory failure and chest sepsis are the commonest causes of death in patients with ALS.

Treatment

Three agents have been approved as disease-modifying treatments for ALS by the FDA. Riluzole is a glutamate receptor antagonist and has been used for the treatment of MND since 1995. It has only a modest effect on survival.[3]

Edaravone intravenous infusion was approved for use by the FDA in 2017 and the oral suspension in 2022. It is not yet available in Europe, where it is considered investigational, due to the need for more data on long-term efficacy. It is thought to act as a free radical scavenger with consequent reduction of oxidative stress, a potential driver of progression in ALS.[4] Approval was based on reduced progression of disability over 24 weeks in a placebo-controlled phase 3 study of patients with early and mild disease.[4] It requires intravenous infusions 10–14 days out of every 28 days, which is a significant burden on patients and carers. Patients can switch between intravenous and oral suspension dosing and maintain the same dosing schedule.

Sodium phenylbutyrate/taurursodiol (PB/TURSO)/AMX0035 was approved by the FDA in 2022 following results of a phase 3 randomized, double-blind trial that highlighted a slower rate of decline in assessment of daily function and longer survival.[5,6] The approval was controversial due to the small size of the trial (n = 137). The mechanism of action of PB/TURSO in ALS is suggested to be prevention of neuronal death through reduction in endoplasmic reticulum stress and support of mitochondrial bioenergetics.[5] Unfortunately PB/TURSO/AMX0035 failed to meet the phase 3 trial primary end-point and is being removed from the market at time of printing.

Predominantly symptomatic and supportive treatments are the mainstay of management (see Table 9.1).[1] Enlisting the support of multidisciplinary health professionals, such as physiotherapists, speech therapists, and palliative care specialists, early on is crucial. Non-invasive ventilation can improve quality of life and survival if tolerated.[1,2] Insertion of percutaneous gastrostomy tubes for ongoing feeding requirements can also be considered.

Disease-modifying treatments

- Riluzole: 50 mg bd.
- Edaravone: Initial cycle: 60 mg IV infusion daily for 14 days, followed by a 14-day drug-free period. Subsequent cycles: 10 out of 14 days, followed by 14-day drug-free periods.
- Sodium phenylbutyrate/taurursodiol: Initial dosage: 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) orally once daily for the first 3 weeks. Maintenance dosage: 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) orally twice daily thereafter.
- Tofersen: Antisense oligonucleotide (ASO) therapy for SOD1-ALS. See Neurogenetics, Chapter 22 p. 303.

Table 9.1 Symptomatic therapies for ALS/MND

Symptom	Treatment
Dysarthria	Speech therapy Whiteboard Electronic communication devices
Sialorrhoea	1% atropine eye drops given sublingually Amitriptyline 10 mg nocte Hyoscine hydrobromide 300 micrograms tds or 1 mg/24 h transdermal patch Glycopyrronium bromide Botulinum toxin/irradiation
Thick pharyngeal secretions	Carbocysteine 375–750 mg qds Pineapple juice
Cramps	Carbamazepine (initially 100 mg daily) Quinine 300–325 mg bd
Spasticity	Baclofen Tizanidine Gabapentin
Emotional lability	Amitriptyline SSRIs
Fatigue	Modafinil 200 mg daily

Evidence base

A Cochrane review of the use of riluzole in ALS identified four controlled studies that evaluated tracheostomy free survival in ALS.[7] It concluded that median survival was increased by about 2–3 months compared to placebo. Both the EFNS and AAN recommend early treatment with riluzole 100 mg daily for ALS. Expert consensus suggests that riluzole is of uncertain benefit for other forms of MND, although it is sometimes used off-licence in these conditions.

Two phase 3 RCTs have investigated the use of edaravone in ALS.[8,9] The first study, a placebo-controlled RCT of 246 patients did not show any change in the progression of ALS over a 24-week treatment period.[8] A post-hoc analysis of this study led to a second phase 3 placebo-controlled RCT of a more restricted group of 134 patients with ALS.[9] The study only included patients who were independent in their ADLs and who were diagnosed with ALS for less than 2 years. After the 24-week treatment period there was a modest, but statistically significant, reduction in the degree of deterioration between the two groups. The ALSFRS-R score changes were –5.01 vs. –7.01 in the treated vs. placebo group.

Sodium phenylbutyrate/taurursodiol (PB/TURSO, AMX0035) was shown in a phase 2 randomized, double-blind, placebo-controlled study evaluating PB/TURSO in 137 patients with ALS over 24 weeks. It found PB/TURSO resulted in a slower rate of functional decline as measured by the

ALSFRS-R scale compared to placebo. The difference was 2.32 points on the 48-point scale over 24 weeks.[5] The open-label extension of CENTAUR evaluated long-term survival in patients who continued on PB/TURSO. It found a median survival difference of nearly 8 months compared to an external placebo group (25 vs. 17 months median).[6] Subsequent post-hoc analysis of CENTAUR found significantly longer time to tracheostomy, permanent assisted ventilation, and hospitalization for PB/TURSO patients vs. placebo over a median follow-up of 35 months.[10] The phase 3 PHOENIX trial however showed that the primary endpoint was not met with no significant difference observed between participants treated with AMX0035 and placebo in ALSFRS-R total score change from baseline at week 48 ($p = 0.667$). No significant difference was observed in the subset of participants who met the CENTAUR trial criteria. There were also no significant differences observed across secondary endpoints.

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Chapter 10

Disorders of muscle

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Introduction

Disorders of muscle comprise a diverse group of both acquired and inherited conditions. This chapter is not intended to cover the whole extent of muscle disease but rather to focus on disorders which have specific disease-modifying or symptomatic treatments.

For the acquired inflammatory disorders immunosuppressive treatments are the mainstay of pharmacological therapy.[1,2] The evidence for these treatments is often based on trials treating inflammatory myositis as a pooled group. Recent advances in the identification of disease-specific autoantibodies and histopathological features have allowed this group to be split into sub-categories.[3] Current treatment algorithms for the different disorders are similar, with variations based on the outcome of long-term cohort studies and clinical experience. However, treatments specific to different sub-categories are in development, including biologic agents targeting T- or B-cell function.

The inherited myopathies are a broad group of disorders that are characterized by inherited muscular weakness. These have traditionally been divided on a pathological basis into dystrophic and non-dystrophic forms depending on their muscle biopsy findings, i.e. fibre type disproportion and structural abnormalities in non-dystrophic forms and fibrosis, fibre hypertrophy, and atrophy in dystrophic forms, although there is overlap. The clinical features of these conditions are determined by their effects on skeletal muscle, as well as other organ systems such as cardiovascular and respiratory systems. The degree of involvement depends on the individual disease. Patient assessment needs to be comprehensive as supportive care with careful monitoring of cardiovascular and respiratory function, physiotherapy, and occupational therapy can make a significant difference to quality of life and survival. This is particularly important given that disease-modifying therapies are not available for the majority of these disorders. Fortunately, this is beginning to change with the advent of genetic approaches. For example ataluren and three antisense oligonucleotide therapies have already been approved for the treatment of Duchenne's in certain countries and many more genetic therapies are undergoing clinical trials for Duchenne's, facioscapulohumeral dystrophy, and centronuclear myopathy.

Disorders for which disease-specific treatments are currently available (mitochondrial disorders and Duchenne's muscular dystrophy), or where symptomatic treatments are beneficial (myotonia and periodic paralysis) are the main focus of this chapter. A more comprehensive overview of the mechanism of action of genetic therapies is included in the neurogenetics chapter (Chapter 22).

Idiopathic inflammatory myopathies

The idiopathic inflammatory myopathies (IIM) are a rare group of disorders, characterized by histopathological findings of inflammation on muscle biopsy. For the most part, an underlying immune-mediated process is thought to drive the primary disease process, although this may not be the case for sporadic inclusion body myositis.

The field is rapidly evolving, in terms of the clinico-pathological understanding of the conditions and the available therapeutic options. Over the last 10–20 years, a number of myositis-specific antibodies and new histopathological markers have facilitated differentiation of many of these conditions. As such, many of the more widely known classifications, e.g. the EULAR/ACR criteria are in need of revision. For the purposes of this summary, the conditions are divided into four main groups based on clinical, serological and pathological features: dermatomyositis; inclusion body myositis; immune-mediated necrotizing myopathy; and anti-synthetase syndrome. Polymyositis is still referenced in a number of the classifications but based on auto-antibody and histopathological features, these patients can mostly be re-classified into one of the above four groups 'Overlap syndromes' with myositis as a feature of other connective tissue disorders will also be discussed. It is being increasingly recognized that individual antibodies have specific profiles both in terms of clinical associations (e.g. the likely rate of malignancy) and response to treatment, hence treatment algorithms may well evolve over the next few years to incorporate this.

Dermatomyositis

Dermatomyositis (DM) accounts for approximately 20% of cases of myositis. Patients typically present with a subacute onset of symmetrical, proximal weakness. There may be myalgia, dysphagia, and neck flexion weakness, and rarely facial or respiratory muscle involvement. Serum creatine kinase (CK) is usually elevated (up to 100 times normal) but is normal in 10%. In DM, skin changes usually precede or accompany the weakness and include: a heliotrope rash, the shawl sign, alopecia, and the presence of Gottron's papules over the knuckles. Subcutaneous calcification and contractures can also occur, particularly in children.

More than 20% of cases are associated with a variety of malignancies. Up to 70% of such cancers are of the cervix, lung, pancreas, bladder, ovaries, or stomach, and these all confer a worse prognosis.

There is a variable association with interstitial lung disease (ILD), higher with certain antibodies, e.g. 90% of patients with anti-MDA5 antibody have interstitial lung disease which may require escalation of therapy irrespective of the severity of the myositis.[7]

Definitive diagnosis was classically made with muscle biopsy which shows perifascicular atrophy and a perivascular inflammatory cell infiltrate. Increasingly the diagnosis can be made on the basis of the clinical findings and the presence of myositis-specific antibodies, including anti-Mi2, TiF1γ, NXP-2, and MDA5, tested on line-blot or Western blotting.

Treatment

Detection and treatment of associated malignancy is a priority. The likelihood of malignancy varies depending upon the accompanying antibody and is most commonly seen in association with TIF1γ. DM may respond to treatment with corticosteroids alone, but a combination of steroids and an immunosuppressive agent leads to improved disease control (PRINTO trial) and helps limit development of steroid side effects.

Initial treatment/induction

- *First line*: PO prednisolone (1 mg/kg/day, maximum 80 mg/day) for 3–6 weeks, then gradually tapering according to clinical response and CK level, aiming to wean off by 1 year. An equivalent dose given as 4 weekly pulsed oral methylprednisolone may reduce side effects.
- IV methylprednisolone (0.5–1 g daily for 3–6 days) can be given initially for severe disease, prior to oral prednisolone as above.
- *Rescue therapy (for severe ILD or myositis)*.
- IVIg (2 g/kg over 3–5 days).
- Cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1 g) or rituximab (750 mg to 1 g/m^2/week for 2 weeks).

Maintenance

- *First line*: azathioprine (2–3 mg/kg/day) or methotrexate (15–20 mg/week) to start concurrently with steroids
- *Second line (resistant disease)*: rituximab (750 mg to 1 g/week for 2 weeks) azathioprine combined with methotrexate; or mycophenolate mofetil (0.5–1.5 g bd) combined with azathioprine or methotrexate.
- *Third line*: ciclosporin (3–5 mg/kg/day), tacrolimus (0.1 mg/kg/day), or cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1 g) or IVIg (2 g/kg over 2–3 days, followed by monthly courses with dose tapered to establish the threshold of response);

Additional measures for ILD

- This patient group is particularly susceptible to opportunistic infections, which can be life-threatening. Many recommend prophylactic treatment against *pneumocystis jirovecii* with co-trimoxazole.
- Methotrexate is typically avoided in this group.

Evidence base

Corticosteroid therapy predominates on the basis of clinical experience, despite a lack of good-quality evidence for its use.[4] Methotrexate or azathioprine appear to be equally effective as maintenance therapy and should be started concurrently with steroids. No head-to-head trials have compared the two agents. Patients on a combination of prednisolone and azathioprine have improved functional outcomes at 3 years compared to prednisolone alone, and retrospective studies have shown response rates of up to 80% with methotrexate.

Despite a lack of good-quality evidence, combinations of azathioprine and methotrexate or of either agent plus mycophenolate are occasionally given for refractory cases.

For severe refractory disease, rituximab[5] has demonstrated efficacy in a large placebo-controlled trial, and IVIg[6] has shown effective short-term improvement of resistant myositis in a modest number of trial patients. The evidence base for calcineurin inhibitors and mycophenolate for refractory inflammatory myopathy is weaker and predominantly retrospective. Cyclophosphamide should only be considered in patients refractory to other second-line agents, due to its toxicity.

Sporadic inclusion body myositis

This is more common in men and classically occurs in the sixth decade of life. There is usually insidious, painless, and asymmetric weakness. There is a distinct pattern of weakness, with preferential involvement of quadriceps and finger flexors, flexor digitorum profundus typically being more affected than superficialis. Weakness of ankle dorsiflexion is also relatively common. Facial weakness and dysphagia can occur, the latter in around 50%. Muscle biopsy is required for diagnosis and shows a characteristic combination of degenerative changes (rimmed vacuoles, mitochondrial impairment, and muscle fibre inclusions containing B-amyloid) and excess inflammation (cytotoxic T cell-mediated inflammation including widespread MHC1 upregulation on muscle sarcolemma).

Treatment

- *First line*: Supportive treatment without active immunosuppression. An exercise therapy programme combining both aerobic and resistance work.
- *Second line*: Although some experts consider a trial of prednisolone (1 mg/kg/day) and other immunosuppressants in certain circumstances, immunotherapy should be avoided in the majority of patients.

Evidence base

In contrast to other inflammatory myopathies, sporadic inclusion body myositis (sIBM) is resistant to immunosuppressive treatment.[8,9] A minority of patients may respond to treatment with corticosteroids and immunotherapy, but long-term, randomized controlled trials are lacking for any immunosuppressive agent. The shorter studies that are currently available are discouraging and have been summarized in a number of systematic reviews. An exercise programme combining aerobic and resistance training results in gains in aerobic capacity and strength over the short term. Approaches to reduce muscle degeneration are now being explored. Unfortunately, a recent trial of a myostatin inhibitor (bimagrumab) did not demonstrate clinical improvement.

Immune-mediated necrotizing myopathy (IMNM)

This accounts for approximately 35% of patients with myositis. The condition is characterized by progressive proximal weakness which can be severe. The time course can be very variable, with some patients presenting subactuely over weeks to months and others with a chronic disorder, progressing over several years, which can be mistaken for a limb-girdle muscular dystrophy. Patients with IMNM typically have high CK levels (median peaks ~5000). The muscle biopsy shows severe muscle fibre necrosis and regeneration with minimal inflammation as well as fibrosis and fatty replacement of muscle in chronic cases similar to that seen in muscular dystrophy. Two specific autoantibodies against SRP and HMG CoA reductase are present in most patients.

HMG CoA reductase antibodies are associated with previous use of statins in many though not all patients. In general, associated malignancies are uncommon. Extra-muscular manifestations such as ILD are rare in this condition though some patients with anti-SRP and cardiac involvement have been described.

Treatment

Initial treatment/induction

- Stop any prescribed statins.
- *First line*: PO prednisolone (1 mg/kg/day, maximum 80 mg/day) for 3–6 weeks, then gradually tapering according to clinical response and CK level.
- IV methylprednisolone (0.5–1 g daily for 3–6 days) can be given initially for severe disease, prior to prednisolone as above.
- *Rescue therapy.*
- IVIg (2 g/kg over 3–5 days) may be required in severe or refractory disease.
- Cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1 g) or rituximab (750 mg to 1 g/m^2/week for 2 weeks).

Maintenance

- *First line*: methotrexate (15–20 mg/week for 2 years before gradual taper).
- *Second line (resistant disease)*: rituximab (750 mg to 1 g/week for 2 weeks) or IVIg (2 g/kg over 3 days, followed by monthly courses).
- *Third line*: Other immunosuppressant agents: azathioprine (2–3 mg/kg/day) mycophenolate mofetil (0.5–1.5 g bd), cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1 g) or IVIg (2 g/kg over 3–5 days followed by monthly courses with dose tapered to establish threshold of response).

Evidence base

The treatment recommendations listed above are derived from the European Neuromuscular Center (ENMC) treatment guidelines 2017,[10] which are based on case series and observational studies. No randomized controlled studies have been undertaken. These studies suggest 10–20% of patients with HMG CoA reductase antibodies have a significant improvement in CK levels and strength on stopping the statin alone, although this is often not sustained, with CK elevation and weakness often recurring several months to years later. At the other end of the spectrum, IMNM is commonly refractory to first-line treatments and acute rescue therapy, and IVIg may be required in up to 50% of patients. The use of IVIg may vary depending on the country and local availability. It can be used in combination with corticosteroids and methotrexate to maintain long-term remission as a second-line therapy, but in the UK it is more commonly used as a rescue therapy if methotrexate or rituximab fails.

Anti-synthetase syndrome

The anti-synthetase syndrome (ASS) accounts for about 15% of cases of myositis. ASS is an autoimmune inflammatory condition associated with autoantibodies targeting an aminoacyl transfer RNA (tRNA) and exhibiting common clinical features. These features include interstitial lung disease, myositis, non-erosive arthritis, unexplained fever, Raynaud's and 'mechanics hands'. It is not uncommon for other clinical features, most commonly interstitial lung disease to dominate the clinical presentation, with minimally symptomatic or asymptomatic myositis. In one study ILD was present in 83% of ASS patients and myositis in 73%. More than 10 ASS antibodies have been described, the most common is anti-Jo1 antibody. Different antibodies often correlate with variations in the clinic picture, e.g. anti-PL7 and anti-PL12 are associated with severe ILD and consequently a poorer prognosis. Associated malignancy is considered very rare.

Treatment

Initial treatment/induction

- *First line*: PO prednisolone (1 mg/kg/day, maximum 80 mg/day) for 3–6 weeks, then gradually tapering according to clinical response and CK level.
- IV methylprednisolone (0.5–1 g daily for 3–6 days) can be given initially for severe disease, prior to prednisolone as above.
- *Rescue therapy (typically for severe ILD)*.
- IVIg (2 g/kg over 3–5 days) may be required in severe or refractory disease.
- Cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1 g) or rituximab (750 mg to 1 g/m^2/week for 2 weeks).

Maintenance

- *First line*: azathioprine (1.5–2.5 mg/kg/day), tacrolimus (0.1 mg/kg/day) or mycophenolate mofetil (0.5–1.5 g bd) as steroid-sparing agents.
- *Second line (resistant disease)*: rituximab (750 mg to 1 g/week for 2 weeks) or cyclophosphamide (2- to 4-weekly IV pulses of 0.5–1 g).

Additional measures for ILD

- This patient group is particularly susceptible to opportunistic infections, which can be life-threatening. Many recommend prophylactic treatment against *pneumocystis jiroveci* with co-trimoxazole.
- Methotrexate is typically avoided in this patient group.

Evidence base

The treatment recommendations are extrapolated from the wider management of myositis and related ILD. Corticosteroids are widely used first line, although there are no controlled studies supporting their use. Over 75% of patients will develop resistance, or relapse when the dose is lowered and hence a steroid-sparing agent is typically used from the start. Azathioprine, mycophenolate, and tacrolimus are widely used steroid-sparing agents on the basis of their known immunosuppressive effects and experience from case series or small controlled trials. There are no comparator studies.

Methotrexate is effective in the management of myositis but is rarely linked to drug-induced pneumonitis, which can cause difficulties in assessing the response to treatment in patients with ILD, so it is typically avoided in this group.

Evidence for the use of cyclophosphamide and rituximab for refractory or rescue therapy mainly arises from small case series and a systematic review. Cyclophosphamide is generally considered to take effect more quickly than other immunosuppressants and hence is often considered in early severe disease where rapid disease control is required. Its significant side effect profile means that it is infrequently used as a maintenance therapy.

Overlap myositis

Overlap myositis refers to a poorly defined sub-group of patients with an inflammatory myositis occurring alongside a connective tissue disease, or with a myositis-associated autoantibody, e.g. anti-Ku, anti-PM/Scl. These antibodies differ from the auto-antibody mentioned already in that they are not 'specific' to myositis and can occur in a number of other connective tissue diseases, whilst the myositis-specific antibodies are found only in idiopathic inflammatory myopathies. The main associated connective tissue diseases are systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome in descending order of frequency. As with all antibody tests there is a false positive rate and the clinical context is crucial to interpretation.

Treatment algorithms for overlap myositis are poorly defined and patients are typically treated by the algorithm corresponding to the dominant symptom complex, e.g. therapies used for rheumatoid arthritis if this is the more severe presentation or drugs for idiopathic inflammatory myopathies (see DM algorithm) if the reverse is true. Ideally agents are selected that have demonstrated effectiveness in both conditions.[11]

Close liaison with the rheumatology team is recommended as certain connective tissue diseases can have important caveats to typical primary idiopathic inflammatory myopathy treatments. For example, the risk of scleroderma renal crisis is higher in patients started on corticosteroids. The risk of this can be better evaluated by the distribution of the disease and in some cases by specific antibody profiles, i.e. the risk is higher with diffuse rather than localized cutaneous systemic sclerosis and if a patient has co-morbid RNA polymerase III related antibodies. Depending on the scenario, alternative immunosuppressive treatments such as methotrexate can be trialled from the onset or appropriate blood pressure and urinalysis monitoring can be instituted with early addition of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers if required.

Mitochondrial disorders

Mitochondrial disorders originate from genetic defects in nuclear or mitochondrial DNA. The clinical presentations are highly variable and patients can present with either symptoms constrained to one organ system e.g. deafness or visual impairment, or a multisystem presentation with a wide spectrum of clinical features, including short stature, ataxia, ophthalmoplegia, deafness, epilepsy, and cardiac conduction defects. Myopathy is a common feature and can present as generalized proximal weakness or in focal forms such as chronic progressive external ophthalmoplegia. A specific molecular genetic diagnosis is frequently possible using a combination of clinical, biochemical, histopathological, and genetic assessments.

Management is predominantly supportive as disease-modifying options are limited. A good understanding of the different systems commonly involved in mitochondrial disease and the specific risks for individual genetic mutations is critical. Symptomatic treatments, e.g. implantable devices for patients at risk of arrhythmia, laxatives, and anti-seizure medications, can improve a patient's quality of life and survival. Management is often best coordinated by a specialized team.

A number of vitamins and other oral supplements may also be considered on a trial basis. There is little evidence to suggest efficacy across the whole spectrum of mitochondrial disease but a beneficial role in specific genetic deficits is likely, although difficult to prove in the form of clinical trials given the small patient numbers and the need for long-term data. There is also evidence of varying quality that certain drugs should be avoided (see Table 10.1).

Treatment

Adjunctive treatment of mitochondrial disease

- Respiratory chain cofactors: co-enzyme Q10 (CoQ10) 5–30 mg/kg daily, maximum 1200 mg daily, is often trialled. It may be of benefit in patients with mitochondrial myopathy due to CoQ10 deficiency.
- Riboflavin 100–400 mg/day should be given in patients with ACAD9 associated complex I deficiency-related myopathy at doses of between 100–400 mg/day.
- Exercise programmes are safe and moderately effective.
- Identification and management of systemic manifestations of mitochondrial disease including cardiac arrhythmias and gastrointestinal dysmotility.

Acute treatment of stroke-like episodes

- Early recognition and good supportive care are critical. This includes aggressive seizure control (avoiding valproate), adequate hydration and

Table 10.1 Drugs to use with caution in mitochondrial disease

Drug	Comment
Sodium valproate	Can cause liver failure in DNA polymerase subunit gamma (POLG)-related disorders and is contraindicated in this group. It may also aggravate seizures in other mitochondrial disorders and hence is generally best avoided
Linezolid/Metformin/Topiramate	Potential for exacerbating lactic acidosis
Aminoglycosides	Increased risk of hearing loss
Statins	Patients may be more prone to statin myopathy, atorvastatin may have a lower risk than simvastatin

nutrition, avoidance of constipation, and treatment of any triggering systemic illness. The Mitochondrial Medicine Society[12] recommend early use of L-arginine 500 mg/kg IV infusion every 6 h for up to 3 days, however the quality of the evidence base supporting this is debated. Early liaison with a specialist unit is advised. In the UK: www.mitochondrialdisease.nhs.uk.

Evidence base

Many agents have been trialled in mitochondrial disease[13] including antioxidants, levocarnitine (*L*-carnitine), creatinine, riboflavin, and folate. Their effectiveness has not been borne out in small studies or clinical practice. Exercise programmes do improve quality of life, strength, and fatigue either as a result of reversal of muscular deconditioning or through direct effects on mitochondrial function.

Mitochondrial diseases are multisystem disorders and cardiac and other organ manifestations are potentially life-threatening. These should be screened for and managed depending on the underlying molecular diagnosis.

Specific therapies trialled in mitochondrial disease:

L-arginine

L-arginine is a naturally occurring amino acid which is the physiological precursor of nitric oxide (NO). It has an important role in endothelial vascular relaxation, which may underlie its mechanism of action. A single non-randomized trial involving 24 patients showed that *L*-arginine significantly reduced symptoms (headache, nausea, vomiting, teichopsia) during acute stroke-like episodes. Further larger studies are required to verify the potential significance of this.

Co-enzyme Q10

Co-enzyme Q10 is an endogenous compound essential for aerobic cellular respiration. It was first used as a treatment for mitochondrial disease in 1986. It is involved in the transfer of electrons between enzyme complexes I, II, and III of the electron transfer chain at the inner mitochondrial membrane and is also an effective oxygen-free radical scavenger. A recent randomized trial evaluated the efficacy of CoQ10 in 30 patients with mitochondrial cytopathy. Compared to placebo, CoQ10 significantly reduced venous lactate after exercise, but clinically relevant endpoints, such as muscle strength, were unaffected. A small meta-analysis including eight trials found no clear evidence to support the use of this and other pharmacologic therapies for mitochondrial disease.[14]

Riboflavin

The ACAD9 gene encodes a complex I assembly protein and is one of the more common mitochondrial causes of cardiomyopathy and myopathy. Riboflavin is a precursor for flavin adenine dinucleotide and flavin mononucleotide which are cofactors for complex I. Supplementation of riboflavin has been demonstrated to improve complex I activity and clinical outcomes for variants of this specific gene in open-label non-randomized studies.

Duchenne's muscular dystrophy

Duchenne's muscular dystrophy (DMD) is an X-linked disorder caused by mutations in the dystrophin gene. It affects 1 in 3500 males and presents with delayed motor milestones in childhood due to proximal muscle weakness. Calf pseudohypertrophy and mild cognitive impairment are other features. Systemic complications include scoliosis, respiratory muscle weakness, dilated cardiomyopathy, and cardiac conduction deficits. The mean age at loss of ambulation is 9 years (range 6–15 years), and patients tend to require assisted ventilation at 19 years (range 14–31 years). The estimated median survival is 35 years. CK is elevated (but may fall to normal levels in adult life). Muscle biopsy shows fibre necrosis and replacement with fat and fibrosis with an absence of dystrophin. Genetic evaluation is needed to confirm the diagnosis and is often used in place of a muscle biopsy in the context of a typical clinical presentation.

Treatment

Disease-modifying agents:

1. *Corticosteroids*

- Prednisolone 0.75 mg/kg/day (max. 30–40 mg/day) or deflazacort 0.9 mg/kg/day (max 36–39 mg/day).

2. *Genetic therapies:*

- Ataluren—for patients with a premature stop codon in the dystrophin gene (~11% of patients).
- Eteplirsen—for patients with a mutation in the dystrophin gene amenable to exon 51 skipping (~13% of patients).
- Golodirsen and viltolarsen—for patients with a mutation in the dystrophin gene amenable to exon 53 skipping (~8% of patients).
- Delandistrogene moxeparvovec—for patients with a confirmed mutation in the *DMD* gene (the Food and Drug Administration (FDA) label stipulated this should be for ambulatory paediatric patients between the ages of four and five. It is not yet available in the UK).

Adjunctive treatments:

- *For ventricular dysfunction*: An Angiotensin-converting enzyme inhibitor and/or β-blocker, implantable cardiac devices.
- *Bone protection*: calcium and vitamin D_3.

Corticosteroid treatment[15–17] is typically started when motor skill development plateaus, usually at 5–6 years, but can be started earlier depending on the patients function although not prior to 2 years old due to potential effects on normal development. It is continued indefinitely if side effects allow. Deflazacort is considered to have similar efficacy to prednisolone with lesser effects on weight gain and bone health, although only small and short-term comparison studies have been undertaken. Larger studies are underway. It has been approved in the USA for the treatment of Duchenne's and is available in the UK and other European countries. Patients taking corticosteroids need to be carefully monitored for side effects, and if weight, behavioural difficulties, or bone health are unmanageable the target dose of prednisolone can be decreased to 0.3 mg/kg/day or given intermittently, e.g. at weekends. These adjustments are thought to be less effective than the typical recommended dose.

An ACE inhibitor and/or β-blocker is indicated if there is evidence of ventricular dysfunction, and bone protection is also required. A stepwise sequence of respiratory interventions is recommended by current guidelines.

Ataluren[18] has been approved by the European Medicines Agency (EMA) for the treatment of Duchenne's and is available under a specialist access scheme in the UK but it has not been approved by the FDA. In contrast eteplirsen, golodirsen, and viltolarsen[19–21] have been approved by the FDA but not by the EMA and are not available in the UK. The mechanism of action of these drugs will be discussed in more detail in the neurogenetics chapter (Chapter 22). In brief, ataluren is a tablet which modulates ribosomal function and may have applications in other genetic diseases. The other three agents are intravenous infusions of antisense oligonucleotides targeting variants in the dystrophin gene, specific to subsets of patients with Duchenne's.

Delandistrogene moxeparvovec[22] is an adeno-associated virus (AAV) vector-based gene therapy. It is a single dose intravenous infusion. It delivers a gene encoding a micro-dystrophin protein, i.e. a shorted version of the normal dystrophin protein. The FDA granted accelerated approval in 2023 based on increased microdystrophin protein present in the skeletal muscles of trial patients. There have been some promising improvements in motor outcomes in phase 1 and 2 studies. Phase 3 studies are currently recruiting.

Evidence base

Corticosteroids

In 2005, the AAN, and in 2008 a Cochrane review, evaluated all RCTs examining the use of corticosteroids in DMD and concluded that prednisone at doses of 0.75 mg/kg/day caused an increase in muscular strength and improved results in standardized functional tests in the short term. Five long-term controlled, non-randomized trials (extending beyond 3 years) with prednisone or deflazacort found that patients could ambulate 1–4 years longer than those not receiving corticosteroids, the need for spinal stabilization surgery was reduced, and the need for non-invasive ventilation delayed. Recent non-randomized trials indicated that corticosteroids may delay the onset of cardiomyopathy. Trials of other immunosuppressive agents (azathioprine, ciclosporin) have not demonstrated any benefit.

Ataluren

Ataluren has been investigated in two randomized controlled trials. These did not show a significant benefit in the overall-intention-to-treat population but did show a benefit in a pre-specified group of patients with a baseline 6 m walking distance (6MWD) between 300 and 400 m. A 2020 meta-analysis of the two RCTs confirmed that ataluren slowed disease progression compared to placebo. This benefit was clearest for patients in the ambulatory transition state of the disease (6MWD 300–400 m) but was present across the whole intention to treat population. The difference between the RCTs and meta-analysis was felt to reflect the short nature of the individual trials (<1 year) and the non-linear progression of patients' 6MWD performances.

Antisense oligonucleotides

Eteplirsen, golodirsen, and viltolarsen were approved under an accelerated access scheme by the FDA, etepliresen in 2016, golodirsen in 2019, and viltolarsen in 2020. The latter two act on the same exon but have a different structure and have been developed by different companies. All three agents have demonstrated increased dystrophin production on serial muscle biopsy in human patients, in short studies (<1 year). Golodirsen and viltolarsen have not demonstrated clinical benefits in randomized controlled trials and hence are subject to ongoing FDA-stipulated conditions, including further clinical trials. High dose eteplirsen showed improvement compared to placebo, but this was in a small study and two patients were withdrawn which may have impacted findings. Its use is also under ongoing evaluation by the FDA.

Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant inherited disorder causing muscle wasting and myotonia (the phenomenon of delayed relaxation of skeletal muscles after voluntary contraction). Myotonic dystrophy type 1 is the commonest cause of adult-onset muscular dystrophy, with a prevalence of 3–15 per 100 000. There is a characteristic facial appearance with ptosis, wasting of the facial and masticatory muscles, and frontal balding. Patients also have sternocleidomastoid and distal limb weakness and wasting. Less commonly, bulbar, respiratory, and extraocular muscles are involved. Myotonia is exacerbated by cold and stress and is usually most pronounced in the face, jaw, tongue, and hands. Associated cardiac pathology (arrhythmia, structural abnormalities, and sudden cardiac death) and impaired respiratory function account for up to 75% of deaths. Excessive daytime sleepiness is common, typically resulting from a combination of obstructive and central sleep apnoea. Cataracts and diabetes mellitus are also common co-morbid conditions. Myotonic dystrophy type 2 (DM2, proximal myotonic myopathy (PROMM)) is a less severe disease with proximal muscle weakness, particularly of the hip girdle muscles, myalgia, stiffness, and fatigue. Definitive diagnosis is by genetic testing, which shows a CTG trinucleotide expansion in DM1 and a CCTG tetranucleotide expansion in DM2.

Treatment

There is currently no effective disease modifying therapies, and management is supportive.[23–25] Annual ECG should be performed, and periodic cardiac and respiratory assessments are important. For further information on recommended multisystem screening and management as well as precautions to take around general anaesthesia, please refer to www.myotonic.org and recent international guidelines.[24]

Myotonia

- Rarely required and only if no cardiac concerns, consider: mexiletine (150 mg/bd–200 mg tds), imipramine (150–200 mg daily), clomipramine (75 mg daily), carbamazepine (up to 600 mg bd), or phenytoin (150–200 mg daily).

- *Daytime somnolence*
- Overnight sleep assessment and non-invasive ventilation if tolerated. If ineffective, consider modafinil (100–400 mg/day).
- *Drugs to avoid/use with caution:*
  1. General anaesthesia: Suxamethonium (succinylcholine) can lead to masseter and laryngo-spasm making intubation difficult. Muscle relaxants are likely to have a stronger and more prolonged effect.
  2. Opiates and other Central Nervous System (CNS) depressants, such as benzodiazepines, can result in type 2 respiratory failure and should be avoided if possible.
  3. Pro-arrhythmic agents (including agents used for myotonia). Agents which are known to prolong the QT syndrome, e.g. antipsychotics and antidepressants should be used with caution with close cardiovascular monitoring.

Evidence base

Small, randomized studies have concluded that mexiletine is superior to placebo in improving grip relaxation time in patients with DM1.[26] Small studies conducted in the 1980s and 90s demonstrated the utility of imipramine and clomipramine. Systematic reviews including a Cochrane review,[25] however, have not found sufficient evidence to support the use of any drugs for myotonia. Treatment for myotonia in DM1 is often not required and mexiletine and tricyclic antidepressants (TCAs) should only be used with caution, depending on a patient's individual risk of arrhythmia.

Non-dystrophic myotonia

The non-dystrophic myotonias are a heterogeneous group of rare inherited skeletal muscle channelopathies that demonstrate clinical and/or electrophysiological myotonia. They are subdivided into myotonia congenita and paramyotonia congenita, depending on their clinical characteristics and whether the genetic variant is of a chloride or sodium channel.

Myotonia congenita

Myotonia congenita (congenital myotonia) is caused by genetic variants in the skeletal muscle voltage-gated chloride channel gene (*CLCN1*), resulting in reduced chloride conductance. Thomsen's disease is transmitted by autosomal dominant (AD) inheritance, and Becker's disease by autosomal recessive (AR) inheritance. Membrane hyperexcitability leads to repetitive firing of muscle fibres, which summate to give clinical myotonia. Myotonia develops following voluntary muscle contraction, often triggered by cold, stress, fatigue, or hunger. Sufferers demonstrate the 'warm-up' phenomenon of improved movement after a few contractions. Patients often have an athletic physique due to muscle hypertrophy from prolonged contraction. The clinical phenotype can vary significantly even in families with the same genetic variant. Certain variants may be more responsive to specific treatments e.g. acetazolamide responsive myotonia congenita, which typically responds well to low-dose acetazolamide.

Paramyotonia congenita

Paramyotonia congenita (Eulenburg's disease) is caused by mutations in the *SCN4A* gene, which encodes a skeletal muscle voltage-gated sodium channel. It has an autosomal dominant pattern of inheritance. The cardinal feature is exercise- or cold-induced myotonia, which worsens with ongoing exercise. This typically affects the eyelids, face, tongue, neck, and hands. CK is elevated, and electromyography shows a significant fall in compound muscle action potential (CMAP) amplitude in cold conditions. As such, patients should be advised to avoid exercising in cold conditions.

Treatment

- *First line*: mexiletine 150 mg bd–200 mg tds.
- *Second line*: lamotrigine 25–300 mg/day, carbamazepine up to 600 mg bd, acetazolamide 125–250 mg BD/TDS, phenytoin 100–250 mg daily or ranolazine 500–1000 mg BD.
- *Third line*: imipramine 150–200 mg/day or clomipramine 75 mg/day.
- *Drugs to use with caution*: suxamethonium and other depolarizing muscle relaxants. Propranolol, beta-adrenoceptor agonists, and adrenaline may aggravate myotonia. Colchicine may cause a myopathy in the context of renal impairment.

Evidence base

Due to the rarity of these conditions, there is a paucity of robust evidence regarding treatment. Nonetheless, a multicentre RCT of 59 patients with non-dystrophic myotonia showed that mexiletine significantly improved stiffness, handgrip myotonia, and quality of life after a 4-week treatment course.[27] One small RCT concluded that lamotrigine reduced myotonia in patients with non-dystrophic myotonia by a third on patient self-assessment scales.[28] There is little controlled trial evidence to support the use of phenytoin and carbamazepine, but clinical experience supports their effectiveness when mexiletine fails. Acetazolamide has been reported to have anti-myotonic properties in small open-label studies; it is also particularly useful in acetazolamide responsive myotonia congenita and in patients where there is clinical overlap with periodic paralysis. Small open-label studies in both non-dystrophic myotonic disorders have suggested ranolazine may also be helpful.[29] Small placebo-controlled cross-over studies have demonstrated improvement of myotonia with imipramine and clomipramine although these are less frequently used now due to more effective and better tolerated options.

Periodic paralysis

The periodic paralyses are a rare group of disorders characterized by episodes of generalized or focal flaccid weakness. They can be divided into primary and secondary forms, depending on whether the disorder is thought to have a purely genetic basis or whether there is an acquired precipitant.

There is overlap, with up to a 1/3rd of patients with thyrotoxic periodic paralysis identified to have loss of function mutations in potassium channels suggesting a possible genetic susceptibility contributing to acquired cases. Renal tubular acidosis and chronic potassium wasting are other potential underlying secondary causes.

The primary disorders are split into three main groups depending on the potassium levels that trigger attacks and additional clinical features: hypokalaemic periodic paralysis, hyperkalaemic periodic paralysis, and Andersen–Tawil syndrome. They are all inherited in an autosomal dominant fashion.

Hypokalaemic periodic paralysis

Hypokalaemic periodic paralysis is caused by several different rare variants in genes coding for skeletal muscle calcium (*CACNA1S* in 70% of patients), sodium (*SCN4A*), and potassium (*KCNE3*) channels. The incidence is ~1 in 100 000. Attacks of extreme generalized weakness lasting hours to days can occur, in association with a fall in serum potassium. Attacks are precipitated by carbohydrate- or sodium-rich foods, rest after exertion, cold, and alcohol. Interictally, there is no myotonia and a normal serum potassium. Patients may develop proximal weakness in their 40s or 50s, by which time the acute attacks tend to have subsided.

Hyperkalaemic periodic paralysis

Hyperkalaemic periodic paralysis is caused by variants in the *SCN4A gene*, encoding a component of skeletal muscle sodium channels. Incidence is 1 in 200 000. Attacks of episodic generalized or focal weakness and myotonia begin in childhood, increase in frequency up to age 50, and decline thereafter. Attacks occur in association with a rise in serum potassium to >4.5 mmol/L. They commonly occur on waking and are typically short, usually <1–2 h. Interictally, myotonia is present in some patients, but serum potassium is normal.

Andersen–Tawil syndrome

Andersen–Tawil syndrome is characterized by periodic paralysis with variable potassium levels, cardiac arrhythmia, and characteristic facies, dental anomalies, clinodactyly, and syndactyly. It is caused by a variant in the *KCNJ2* gene.

General principles of management of periodic paralysis

1) Treatment of any underlying systemic abnormality, e.g. thyrotoxicosis or renal tubular acidosis.
2) Abortive treatment: aimed at rapidly normalizing potassium during acute attacks. Secondary causes such as thyrotoxicosis are typically associated with hypokalaemia and this can be managed acutely as per primary hypokalaemic forms. Andersen–Tawil syndrome can have low, raised, or normal levels of potassium and acute management is led by the individual's ictal potassium levels. Patients with normokalaemic periodic paralysis are treated as per the hyperkalaemic pathway.
3) Preventative treatment: A combination of trigger avoidance, dietary modifications and agents such as carbonic anhydrase inhibitors

(acetazolamide and dichlorphenamide) or long-term potassium-sparing or depleting agents.

4) Treatment of associated clinical features, i.e. the high risk of arrhythmia with Andersen–Tawil syndrome.

Treatment of periodic paralysis associated with hypokalaemia

Treatment

Acute attacks

- PO potassium replacement: 30 mEq potassium chloride (KCl) every 30min (not delayed release formulations) up to a max of 200mEq/day. If hospitalized or severe, KCl can be given intravenously but should be given with mannitol (not normal saline or dextrose, which can exacerbate the paralysis). Typically give 10 mEq every 30 min and monitor serum potassium closely for 24 h to assess for rebound hyperkalaemia. Milliequivalents are used to avoid confusion between formulations. 1500 mg oral KCl equates to 20 mEq. Take the oral supplement with water and not sports drinks which often have high sugar and sodium content and can worsen the paralysis.

Prophylaxis of attacks

Attacks may be prevented by a low-carbohydrate, low-sodium diet, and avoidance of alcohol and vigorous exercise. A potassium supplement can also be considered prior to known triggers.

- *First line*: carbonic anhydrase inhibitors (acetazolamide 250 mg bd or diclofenamide 50 mg bd) or slow release KCl formulations (not more than 100 mEq/day).
- *Second line*: potassium-sparing diuretics (spironolactone 25–100 mg daily, eplerenone 50–100 mg/day or triamterene 50–150 mg daily).

Evidence base

Acetazolamide reduces frequency and severity of attacks in about half of patients. This varies depending on the underlying mutation. It is most effective in patients with a calcium gene mutation and less effective in patients with a sodium gene mutation. Treatment may cause paradoxical worsening in 10% of patients, especially those with co-morbid diabetes and thyrotoxicosis. The evidence base for use is derived from clinical experience and small non-randomized studies. Diclofenamide has been assessed in the context of several small randomized clinical trials and has a significantly beneficial effect on attack frequency and severity, with a milder side effect profile than acetazolamide. As second-line therapy, potassium-sparing diuretics may be useful alternatives based on open-label studies.

Treatment of periodic paralysis associated with hyperkalaemia

Treatment

Acute attacks

Attacks are brief and often do not need treatment. One to two inhalations of salbutamol or an oral carbohydrate load may attenuate attacks. Severe hyperkalaemia is unusual (potassium is considered elevated in the context of periodic paralysis if >4.5 mEq/L, or 4.5 mmol/l, which may be in the normal ranges for most labs) but should be treated as per local protocols.

Prophylaxis of attacks

Attacks may be prevented by frequent carbohydrate-rich meals, avoidance of fasting and added dietary potassium, or drugs known to increase serum potassium.

- *First line*: carbonic anhydrase inhibitors (acetazolamide 250 mg bd or diclofenamide 50 mg bd).
- *Second line*: thiazide diuretics, e.g. hydrochlorothiazide 25–50 mg/day.

Evidence base

Diclofenamide was shown to significantly reduce the rate and severity of attacks of hyperkalaemic periodic paralysis in 2 randomized, double-blind cross-over studies.[30] Acetazolamide and thiazide diuretics are used on the basis of clinical experience and small studies.

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Chapter 11

Disorders of the neuromuscular junction

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Introduction

Disorders of the neuromuscular junction (NMJ) are divided into acquired (typically autoimmune) and hereditary causes. Myasthenia gravis (MG) is by far the most common NMJ disorder. Lambert–Eaton myasthenic syndrome (LEMS) is also discussed here. NMJ dysfunction due to *Clostridium botulinum* infection is covered in Chapter 18, Neurological infections.

The congenital myasthenic syndromes (CMS) are a rare group of inherited disorders that typically present early in life with fatiguable muscle weakness. Whilst there are no disease modifying or genetic therapies for the treatment of CMS, several agents can be used, which facilitate transmission at the NMJ. The benefits are often gene-specific and are summarized in the CMS sub-section.

Myasthenia gravis

MG is the most common NMJ disorder. It is an antibody-mediated autoimmune disorder with an estimated prevalence of ~15 per 100 000 individuals. The pattern of muscle involvement can vary, but characteristic early features include asymmetric ptosis and diplopia secondary to extra-ocular muscle involvement. Other commonly affected muscles include bulbar, facial, jaw, neck, and proximal limb muscles. It is important to recognize the history of fatiguability during repeated motor actions, e.g. ptosis that develops hours after waking and resolves with rest. This distinguishes MG from the persistent fatigue that can be seen in other neurological disorders. Fatiguability can also be demonstrated on clinical examination. The majority of patients have generalized myasthenia, and fewer than 15% have purely ocular involvement. Importantly there is potential for neuromuscular respiratory failure, termed 'myasthenic crisis'.

Over 80% of patients with generalized MG have circulating pathogenic autoantibodies directed against the nicotinic acetylcholine receptor (nAChR) at the post-synaptic membrane. A small proportion of patients have anti-MuSK, anti-LRP4, or low-affinity antibodies binding to nAChRs.

Myasthenia has a bimodal age of onset. Early-onset disease typically affects women under 40, whereas late-onset myasthenia is more common in men. Thymic hyperplasia is seen in most early-onset cases. Thymoma is present in about 15% of patients, most between the ages of 40–60 years.

Diagnosis is primarily clinical and serological. Characteristic neurophysiological findings are decremental compound muscle action potentials (CMAPs) on repetitive nerve stimulation and increased jitter and block on single-fibre EMG. CT or MRI of the thorax is required to investigate for thymic hyperplasia and thymoma.

Treatment

Symptomatic therapy

- *First line*: pyridostigmine 30–90 mg every 4–8 h. Benefit typically lasts 3–4 h and the treatment is symptomatic only hence administration typically mirrors diurnal profile of symptoms. Recommended maximum 450 mg/24 h—higher doses may risk cholinergic crisis. MG secondary to anti-MuSK antibodies is typically less responsive to cholinesterase inhibitors.

Immunomodulatory therapy

Acute/induction

- *First line*: prednisolone.
- *Second line*: IVIg 1–2 g/kg over 2–5 days or plasma exchange (PLEX) (MuSK MG may respond better to PLEX).
- *Third line*: Rituximab 1 g given twice, two weeks apart or newer immunotherapies (eculizumab, ravulizumab, efgartigimod).
- Also see Myasthenic crisis, p. 167

Chronic/maintenance

Strategies for long-term treatment of myasthenia gravis vary worldwide depending on local and national experience, as well as the availability of newer immunotherapies. We have listed possible treatment options below but acknowledge that, particularly for the older oral immunotherapies, there may be low level evidence for use in myasthenia.

Oral immunotherapies:

- Azathioprine 50 mg daily, increased to a maintenance dose of 2–3 mg/kg over 1 month.
- Methotrexate 10 mg once weekly, increased to 20 mg weekly at 4 weeks (along with folic acid 5 mg once weekly).
- Mycophenolate mofetil 500 mg bd, increased to 1 g bd after 4 weeks, or methotrexate 10 mg once weekly, increased to 20 mg weekly at 4 weeks (along with folic acid 5 mg once weekly).

Rituximab:

- Rituximab 1 g given two weeks apart. This can be continued at 6–12 monthly intervals depending on clinical response and other immunological biomarkers (see drug monograph p. 701)

Newer immunotherapies:

- *Complement inhibitors*: Eculizumab 900 mg IVI weekly for 4 weeks, followed by 1200 mg fortnightly. Ravulizumab: Initial loading dose of 2400–3000 mg day 1, 3000–3600 mg on day 15 then every 8 weeks.
- *FcRN inhibitors*: Efgartigimod: 10 mg/kg IVI once weekly for 4 weeks followed by intermittent 4-week cycles based on clinical response.

Surgical treatment

- Thymectomy. (See next)

Drugs to avoid/use with caution

See Box 11.1, which lists medications that could exacerbate weakness or trigger myasthenic crisis. A useful up to date list is also available on www.myaware.org.

Evidence base/Guidance for the use of immunosuppression

- Both the American Academy of Neurology[1] and Association of British Neurologists (ABN)[2] have released comprehensive guidelines for the management of myasthenia gravis. These are broadly similar and summarized in this chapter.

Box 11.1 Drugs to avoid/use with caution in myasthenia gravis

- *Anaesthetics*:
  - depolarizing neuromuscular blockers: suxamethonium.
  - non-depolarizing neuromuscular blockers: pancuronium, etc.
- *Antiarrhythmic agents*:
  - quinidine, quinine, procainamide.
- *Antibiotics*:
  - aminoglycosides: gentamicin, amikacin, etc.
  - quinolones: ciprofloxacin, norfloxacin.
  - tetracyclines: doxycycline, minocycline.
- *Antihypertensives*:
  - beta-blockers, calcium channel blockers.
- *Antimalarials*:
  - chloroquine.
- *Antirheumatics*:
  - chloroquine, hydroxychloroquine, penicillamine.
  - *Botulinum toxin*.
- *Chemotherapy*:
  - cisplatin.
- *Neuropsychiatric drugs*:
  - lithium, chlorpromazine, phenytoin.

Symptomatic treatment:

- Pyridostigmine has not been trialled in a prospective, randomized fashion. However, in view of overwhelming clinical experience, it remains the first-line therapy. Neostigmine is occasionally used in intensive care settings but is shorter acting. It should be noted that high doses of pyridostigmine can lead to desensitization of acetylcholine receptors, inducing muscle weakness and a cholinergic crisis. This can be difficult to distinguish clinically from a myasthenic crisis (see details on cholinesterase inhibitors under Myasthenic crisis, Symptomatic treatment, p. 167).

Immunomodulation:

- Most patients with generalized disease will not achieve adequate response to pyridostigmine alone and require immunosuppression.

Induction of remission:

- Corticosteroids are the most used short-term immunosuppressant therapy. It is recommended that prednisolone is started at a low dose (typically 5–10 mg/day). It is gradually titrated up by 5–10 mg every 3 days to avoid the 'steroid dip' in symptoms sometimes seen 4–10 days after starting high-dose prednisolone. There is no clear maximum dose although the ABN guidelines recommend 1.5 mg/kg or 100 mg alternate days.[2] Practically the dose is typically escalated until symptoms resolve or the maximum dose is reached. A 2-week trial at each dose is suggested to determine its efficacy. Alternate day dosing is recommended in the ABN guidelines based on lower corticosteroid-related side effects, although the level of published evidence supporting this approach is limited and it can be a difficult regimen for patients to adhere to.

- The dose can then be slowly reduced after a period of stability. Withdrawal of pyridostigmine prior to prednisolone is recommended to test whether the condition is truly in remission. Prednisolone results in remission or significant improvement in up to 80% of patients.
- Steroid-sparing agents are commonly started early or even concurrently with prednisolone, but this may result in a prolonged treatment course for the small proportion of patients who enter remission on corticosteroids and remain so on their withdrawal. Hence, there is an argument to only start steroid-sparing agents if patients relapse whilst corticosteroids are being withdrawn.
- The authors' approach is to reduce prednisolone as tolerated. If a dose of 7.5 mg/day or less is achieved prior to relapse, then long-term low-dose prednisolone can be considered a maintenance therapy. If this dose cannot be reached, then a steroid sparing agent is started.
- Rapid short-term remission can be achieved with IVIg or PLEX in severely affected individuals or to optimize disease activity prior to surgery. The two treatments were demonstrated to be equally efficacious in a single RCT in moderate to severe MG.[3,4] Choice is largely dictated by ease of access and side effect profile.

Maintenance immunotherapy:

1) Oral immunotherapies:
    - Azathioprine is recommended as the first-line agent by the ABN in their 2015 guidelines,[2] although this may well change if the use of newer immunotherapies becomes more established. It may not be the most widely used agent worldwide, where clinical experience and availability of newer immunotherapies may vary. There is good evidence of efficacy in RCTs, but it has a slow time to onset of clinical effect (>1 year). There is conflicting evidence for the efficacy of mycophenolate and no high-quality published evidence for the use of methotrexate. However, these agents can be trialled if azathioprine fails.[5]
2) Rituximab:
    - A randomized controlled clinical trial: The RINOMAX trial included 47 patients with new onset generalized myasthenia gravis. Patients were randomized to a single dose of rituximab 500 mg or placebo. The primary outcome of minimal disease at 16 weeks was reached by 71% of patients treated with rituximab, compared with 29% of the placebo group ($p = 0.007$).[6]
    - A small subgroup of ~10–30% of patients with myasthenia are estimated to be refractory to conventional oral immunosuppression and several single-armed studies have demonstrated that rituximab may be effective in this situation. A meta-analysis, published in 2021 identified 24 studies, involving 417 patients. Minimal disease manifestation status was achieved in 64% of patients (95% CI 49–77%)[7] A large randomized controlled trial is required to obtain more accurate efficacy data.

  - Rituximab has been authorized by NHS England for use in patients with 'explosive' disease onset generalized myasthenic crisis, where first-line rescue therapies such as corticosteroids, plasma exchange, and IVIg have been ineffective.[8] The evidence base for use in this scenario is limited to clinical experience and small non-randomized studies. Patients with MuSK-positive disease are more likely to be refractory to standard therapies and rituximab could be considered earlier in these patients.

3) Newer immunotherapies:
  - Several new agents have recently been approved for use in generalized myasthenia gravis with positive nAChR antibodies. Three agents are available in the USA at the time of publication. Both eculizumab and ravulizumab act as potent C5 inhibitors. They have established efficacy in the treatment of paroxysmal nocturnal haemoglobinuria and appear highly effective in the management of myasthenia gravis. Efgartigimod is a first-in-class neonatal Fc receptor inhibitor (FcRn). It has also demonstrated significant efficacy in the treatment of generalized myasthenia gravis.

Their key studies are outlined next:

- A phase III randomized controlled trial (REGAIN) compared eculizumab with placebo in patients with refractory AChR positive generalized myasthenia gravis.[9] The primary endpoint (change in MG-ADL score) was not met at week 26, however multiple secondary endpoints were met. There was a ~66% reduction ($p = 0.0057$) in exacerbations and admissions with eculizumab when compared to the placebo arm. The amount of co-prescribed immunosuppressive therapies was also reduced in the active arm.
- Efgartigimod is indicated for the treatment of patients with AChR antibody positive generalized myasthenia gravis. The ADAPT study was a randomized double-blind, placebo-controlled, phase 3 study of 167 patients.[10] All patients had a MG-ADL score of ≥5 at baseline. Of these 68% of patients on efgartigimod were MG-ADL responders (defined as ≥2 point improvement in MG-ADL sustained over 4 weeks), compared to 30% with placebo ($p < 0.0001$).
- Ravulizumab is indicated for the treatment with AChR antibody positive generalized myasthenia gravis. The CHAMPION-MG study was a double-blind, placebo-controlled, multicenter phase III study of ravulizumab for treatment of generalized myasthenia gravis with nAchR antibodies.[11] The study included 175 patients. There was a statistically significant improvement in the MG-ADL score at week 26 of 3.1 points in the active group and 1.4 points in the placebo group ($p < 0.001$).

Surgery:

- Thymectomy is indicated in all patients with thymoma and has an increasing role in patients without thymoma. It should be considered in all nAChR positive patients with generalized myasthenia up to the age of 65 early in the treatment course. A randomized controlled trial of thymectomy for generalized non-thymomatous MG demonstrated that patients with thymectomy required lower doses of prednisolone and were less frequently hospitalized for MG exacerbations than those who did not have the procedure (hospital exacerbations 9% vs. 37%, $p < 0.001$).[12] The benefits appear to be higher in young patients, in the first 3 years of their disease, with generalized, nAChR antibody positive disease. MuSK-positive patients are not thought to benefit from this procedure.

Myasthenic crisis

This is a life-threatening neurological emergency, characterized by the development of respiratory and bulbar muscle weakness. Mortality is around 4%. Commonly, a crisis is triggered by intercurrent illness or infection, most frequently of the respiratory tract. This can sometimes occur as a direct result of aspiration from undiagnosed bulbar dysfunction. Other precipitants include surgery, pregnancy, tapering of maintenance immunosuppression, emotional stress, heat, hyperthyroidism, and various medications (see Box 11.1).

Supportive management in the form of close monitoring of airway patency and respiratory function is important. Regular forced vital capacity (FVC) assessments are essential. FVCs <1–1.5 L, <50% predicted or a rapid fall in FVCs should prompt review by the intensive care unit (ICU) to consider whether a patient may be at risk of requiring intubation and ventilation.

Treatment

Supportive management

Patients should be admitted to the ICU early, as intubation and ventilation may be required. Should neuromuscular blockade be needed, succinylcholine can be used, although higher doses than normal may be necessary. Non-depolarizing neuromuscular blockers should be used with caution.

Immunomodulatory therapy

- *First line*: IVIg 0.4 g/kg/day for 5 days or PLEX, in addition to prednisolone 60–80 mg od.
- *Second line*: Rituximab 1 g at baseline, repeated at 2 weeks—NHS England have commissioned rituximab for use in ‘explosive’ onset MG where respiratory and bulbar functions are unresponsive to conventional rescue therapies, although the evidence base is limited (see above).

Symptomatic treatment

- Cholinesterase inhibitors: pyridostigmine 60–90 mg 4- to 6-hourly. Cholinesterase inhibitors can increase respiratory secretions rendering it difficult to maintain a clear airway in intubated patients and rarely they can trigger cholinergic crises (doses above 450 mg/24 h should be avoided). If the oral route is not immediately available neostigmine can be used via either SC or IV routes. It has a rapid onset of action and caution should be taken with the first dose where, like the Tensilon test it can precipitate heart block. The doses of oral pyridostigmine and parenteral neostigmine are not directly comparable, 60 mg oral pyridostigmine being roughly equivalent to 500 micrograms of IV neostigmine and 1–1.5 mg of SC neostigmine.

Evidence base

Several prospective trials have shown no significant difference in efficacy between IVIg and PLEX for exacerbations of MG. IVIg may be better tolerated, whilst plasma exchange may have a faster onset of action.[3,4]

Corticosteroids should be started concurrently with IVIg or PLEX, as the effects of these acute therapies are not sustained beyond a few weeks. The risk of a 'steroid dip' may be mitigated by simultaneous use of PLEX or IVIg.

Lambert–Eaton myasthenic syndrome

LEMS is a rare disorder mediated by antibodies against presynaptic voltage-gated calcium channels (VGCCs) at the NMJ. It is five times more common in men than women. Onset is usually over the age of 50 years, with slowly progressive proximal limb weakness, mostly affecting the lower limbs, often mimicking a myopathy, rather than MG, and typically exacerbated by prolonged exercise or hot weather. Autonomic symptoms including dry mouth, dry eyes, and erectile dysfunction may be prominent. Ocular and bulbar symptoms occur less frequently than in MG. Respiratory involvement is rare. About 50% of cases are paraneoplastic, associated with small cell lung cancer (SCLC) (>80%), lymphoproliferative disorders, and rarely other malignancies. Non-paraneoplastic cases are of a primary autoimmune aetiology.

Circulating P/Q type VGCC antibodies are detectable in 85% of patients. In contrast to myasthenia, EMG with repetitive stimulation at 10 Hz shows a characteristic increment of CMAP amplitude (rather than the decrement seen in MG).

Treatment

Treatment of the underlying malignancy may cause symptom regression.

Symptomatic therapy

- *First line*: 3,4-diaminopyridine (3,4 DAP) 15 mg/day, increasing up to 60 mg/day.
- *Second line*: pyridostigmine 60–90 mg every 4–6 h.
- *Third line*: guanidine 5–10 mg/kg/day, increasing up to a maximum of 30 mg/kg. Patients should be monitored for the development of renal toxicity and bone marrow suppression.

Immunomodulatory therapy

- *First line*: prednisolone 1 mg/kg/day.
- *Second line*: Azathioprine, mycophenolate mofetil or a trial of IVIg (2 g/kg), acutely or as maintenance therapy every 1–3 months.
- *Third line*: ciclosporin, rituximab, PLEX.

Evidence base

Symptomatic therapy:

- 3,4-DAP has been shown to improve muscle strength and resting CMAP amplitude in up to 79% of patients. Adjunctive treatment with pyridostigmine may confer additional benefit. Pyridostigmine, when combined with low-dose guanidine (<1 g/day), can be considered, although the evidence is based on several small studies from the 1990s. Alternate day dosing of guanidine may reduce the risk of neutropaenia.

Immunotherapy:

- Patients with non-paraneoplastic LEMS may require long-term immunosuppression, usually with steroids and azathioprine. There are no large-scale trials firmly demonstrating the magnitude of clinical improvement with oral prednisolone or azathioprine, but their use is widespread, following several case series. Corticosteroids may also be of benefit in patients with LEMS due to underlying SCLC. In a randomized cross-over trial, IVIg was shown to significantly improve limb, respiratory, and bulbar muscle strength, compared to placebo. Patients with LEMS may not respond as well to PLEX as those with myasthenia. Isolated case reports support the use of rituximab for resistant cases.

Congenital myasthenic syndromes

The congenital myasthenic syndromes are a heterogenous group of inherited disorders of the neuromuscular junction. They are rare and are thought to have a prevalence of 25–125/100,000. They typically present in early life but may occasionally present for the first time in adolescence or even later. They are classically characterized by fatiguable muscle weakness, however in some cases, there may be minimal clinical fatigability and an individual's phenotype may resemble a limb-girdle muscular dystrophy. Over 30 culprit genes have been identified, which encode proteins involved in acetylcholine transmission at the NMJ. Several of the genes responsible for CMS have important roles outside of the NMJ and hence the phenotype may be complicated by other gene-specific symptoms, e.g. learning difficulties and ataxia.

The evidence for treatments typically comes from clinical experience and small case series. Suggested treatments for the most common conditions are summarized in Table 11.1. Further information can be found in excellent review articles by Finlayson *et al.* (2013)[13] and Finsterer *et al.* (2019).[14] It is important to note that pyridostigmine can worsen some CMS subtypes, notably those related to COLQ and DOK7 mutations.

Table 11.1 Treatment options for congenital myasthenic syndromes

CMS	Gene	1st line Treatment	2nd line Treatment
Acetylcholine receptor deficiency	AChR subunit genes	pyridostigmine	3,4 DAP
Post-synaptic	RAPSN	pyridostigmine	3,4 DAP
Post-synaptic	DOK7	Salbutamol or ephedrine	3,4-DAP (some may show deterioration)
Slow channel	AchR subunit genes	Fluoxetine	Quinidine
Acetylcholine esterase deficiency	COLQ	Salbutamol or ephedrine	
Fast channel	AchR subunit genes	Pyridostigmine	3,4 DAP

Data based on Finlayson S *et al.*[13]

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Chapter 12

Parkinson’s disease and parkinsonism

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Introduction

Parkinsonism is a clinical syndrome characterized by bradykinesia, accompanied by tremor, rigidity, and/or postural instability. It has multiple different causes. Identification of the underlying aetiology is important, as idiopathic Parkinson's disease (PD), the commonest akinetic rigid syndrome, is typically very amenable to symptomatic treatment, whilst other causes of parkinsonism including the common 'Parkinson's plus syndromes' have a much poorer response to dopaminergic therapy.

In this chapter, we will discuss the commonest akinetic rigid syndromes and their treatment. There are also dedicated sub-sections to management of related medication induced complications, such as impulse control disorders (ICDs), dopamine agonist withdrawal syndrome (DAWS), and the closely linked neuroleptic malignant syndrome (NMS) and Parkinson's hyperpyrexia syndrome (PHS).

Parkinson's disease

PD is one of the commonest movement disorders. It has a prevalence of 160 per 100 000 in the general population. Incidence increases with age, and it affects almost 4% of those over the age of 80 years. As well as the classic motor features of the disease, non-motor features have become increasingly recognized. These include dysautonomia (constipation, urinary dysfunction, and orthostatic hypotension), neuropsychiatric disturbance (cognitive dysfunction, depression, and psychosis), and disorders of sleep.

General principles of management

Guidance for the optimal management of PD has been produced by NICE in the UK[1] and the AAN in the USA.[2] A comprehensive evidence-based treatment review has also published by the International Parkinson and Movement Disorder Society (MDS).[3]

As a rule, patients should be referred to a specialist for assessment and confirmation of the diagnosis prior to initiation of treatment. If confirmed, appropriate counselling should be given and advice provided regarding the risks and benefits of medication, as well as the likely natural course of the disease. A minimum of a yearly review is recommended, to ascertain the rate of disease progression, as well as the ongoing effectiveness and side effects of medications.

Patients benefit from access to specialist nurses, as well as physiotherapists, occupational therapists, and speech and language therapists, as appropriate. Given the chronic and progressive nature of the condition, referral to palliative care teams and advanced care planning should be considered, when appropriate.

Treatment of motor symptoms

In early disease, where functional disability has just begun to be problematic and require symptomatic therapy, the decision to initiate treatment is based on clinical factors as well as the patient's preference. The age of onset, severity of motor symptoms, and co-morbidities such as cognitive impairment are key factors to guiding selection of first-line therapy.

Levodopa therapy is the most effective agent for the management of motor symptoms of Parkinson's but its use is associated with the earlier development of motor complications, particularly in patients with young-onset disease (<50 years old). Dopamine agonists and monoamine oxidase inhibitors are more frequently used as first-line agents in this group.

Management of PD in early disease

Several different agents can be used as first-line monotherapy and a tailored approach with detailed patient discussion is recommended.

Treatment

- *First line*: dopamine agonist, levodopa, or MAO-B inhibitor
- *Other*: anticholinergic for prominent tremor

Evidence base

In a large, randomized trial, the PD MED study[4] patients were randomly assigned to levodopa, a dopamine agonist, or a MAO-B inhibitor. Levodopa demonstrated improved patient and clinician rated clinical scores, fewer side effects and better patient related quality of life in both the short and long-term (median follow-up 3 years) compared to the other treatments.

Initial use of dopamine agonists delays the emergence of late motor complications, but side effects can be problematic, particularly impulse control disorders, and symptomatic improvement is often less marked than with levodopa.

Monoamine oxidase B (MAO-B inhibitors) can also be used as a levodopa-delaying therapy, but these agents typically only have modest symptomatic benefit.

Most patients will eventually require levodopa therapy for optimal symptomatic control of motor symptoms. It should be started at the lowest effective dose and increased slowly as required.

Anticholinergics can be used in young patients with intractable tremor but should be avoided in the elderly, due to a greater susceptibility to confusion and other side effects.

Management of advanced PD with motor complications

Motor fluctuations occur in up to 60% of patients after 5–10 years of levodopa therapy. Those with a younger age at onset or taking higher doses of levodopa are at higher risk of developing complications earlier. Motor complications include delayed 'on', prolonged 'off', 'on-off' fluctuations, freezing and the development of involuntary movements such as dyskinesias, and dystonia.

Over time there is an increasingly narrow therapeutic window in which dopamine is effective at providing good control of motor symptoms. Too little dopamine results in 'off' periods and dystonia, whilst too much causes dyskinesias. At this point medications need to be adjusted so that plasma dopamine levels remain within the therapeutic window and fluctuate less.

Increasing off periods

'Off' periods result from several different pathophysiological mechanisms, including:

- Progressive loss of dopaminergic pre-synaptic neurons resulting in reduced dopamine storage and a motor response in line with levodopa pharmacokinetics.
- Impaired gastric-emptying leading to a levodopa response dependent on the timing in relation to meals and the macro-nutrient content of meals.
- Intrinsic post-synaptic changes at the level of the striatum that lead to 'offs' irrespective of 'dopaminergic tone'.

Management of increasing 'off' periods

1. Modification of levodopa therapy:
   - Smaller levodopa doses are given more frequently, avoid taking doses within 60 min of protein-rich meals;
   - Slow-release Levodopa preparations (note 30% reduction in bioavailability requiring dose increase)
2. Adjuncts:
   - COMT-inhibitor, dopamine agonist, istradefylline, or MAO-B inhibitor
3. 'Rescue'/on-demand therapies:
   - Levodopa (dispersible tablets or inhaled formulations) or apomorphine (subcutaneous injection or sublingual)
4. 'Advanced interventions'
   - Apomorphine infusion;
   - Levodopa intrajejunal infusion;
   - Deep brain stimulation (DBS).

Modification of levodopa dose frequency

As the condition progresses, patients begin to develop wearing-off effects, typically at about 3–4 h after their levodopa dose consistent with its known plasma half-life and reflecting progressive loss of dopaminergic neurons. The levodopa dose can be split into 3–4-h intervals to counteract this.

Sustained-release levodopa preparations

Alternatively, sustained-release or combination-release levodopa formulations can be used. Currently two alternatives to immediate release levodopa exist, sustained-release levodopa preparations (e.g. Sinemet® CR, Madopar CR) and combined-release products: (Rytary® which contains both immediate and extended-release carbidopa/levo-dopa). Use of sustained-release agents is complicated by a lack of predictability in the timing of their effect. In addition, due to their reduced bioavailability, compared to immediate release, the dose may need to be increased by up to 30%. A sustained-release preparation given at night may be of use if patients experience poor nocturnal mobility, with difficulty turning over in bed, or 'off' periods on waking.

Use of an adjunct

Other options include the use of agents acting to inhibit dopamine metabolism and thereby prolong its half-life, dopamine agonists which have prolonged activity on post-synaptic receptors and newer agents such as istradefylline, which acts via a non-dopaminergic mechanism to modulate motor complications.

- Dopamine agonists (DAs): see Management of PD in early disease, p. 173;
- MAO-B inhibitors: see Management of PD in early disease, p. 173;
- Catechol-O-methyltransferase (COMT) inhibitors: entacapone is typically used first-line. It comes as a stand-alone preparation or as a single tablet in combination with levodopa and dopa decarboxylase (DDC) inhibitors. Opicapone is a newer once-daily agent. Tolcapone is an alternative but due to the rare risk of fulminant hepatitis, close monitoring of liver function is required, and it is seldom used.
- Istradefylline: A new adenosine A2A antagonist licensed by the FDA in 2019 for patients with motor fluctuations. It has been demonstrated to reduce daily 'off' time compared to patients receiving placebo in 4 RCTs.

Fast acting 'rescue'/On-demand therapies

- Dispersible formulations of levodopa, e.g. dispersible Madopar®. Taken with fluid the dispersible form transits the stomach faster than the typical tablet form, leading to an onset of action at ~25 min compared to the standard form (~45 min). Its duration of action is however shorter.
- Inhalational levodopa—onset of action ~10 min.
- Subcutaneous apomorphine—predominantly for freezing and unpredictable 'offs'—onset of action <10 min.
- Sublingual apomorphine—oromucosal absorption which bypasses the hepatic first-pass effect—time to maximal effect ~30 min.

Evidence base

There are now a wide variety of treatment strategies with typically good evidence base, but little in the way of cross-comparator studies between agents. Treatment options vary in terms of mechanism, route, side effect profile, cost, and ease of use. For the pertinent trials for the agents discussed above please see the relevant drug monographs.

Drug-induced dyskinesias/dystonia

Sixty per cent of levodopa-treated patients develop dyskinesias within 10 years of treatment. During 'on' periods, dyskinesias are commonly choreiform when mild but can be ballistic when severe. 'Off' period dyskinesias are often dystonic.

Dyskinesias often occur at peak dose (60–90 min after the last levodopa dose) or may be biphasic ('trough' and 'peak') when concentrations of levodopa are just below or above the effective range.

Management of drug-induced dyskinesias/dystonia

- The treatment strategy is similar to the management of 'off' periods—an attempt to reduce serum dopamine fluctuations, but with an overall goal of reducing peak serum levels of levodopa. A compromise should be reached between adequate motor control and dyskinesias.
- Amantadine: may be used as an adjunct to levodopa in those with dyskinesias.

Advanced interventions

Deep brain stimulation, intrajejunal levodopa infusion (Duodopa®) and subcutaneous apomorphine infusion are considered 'advanced interventions/therapies' due to their need for surgical procedures or, in the case of apomorphine day-case or inpatient admission to initiate treatment. They are typically used later in the disease course if other therapies are no longer effective at controlling symptoms. Both infusion therapies have a 'boost' function which provides an 'on demand' increment in the dose. This can be used alongside or instead of a background continuous infusion. Apomorphine infusion is not available in all countries.

The evidence base for subcutaneous apomorphine infusion and intrajejunal levodopa therapy is discussed in their respective drug monographs.

Deep brain stimulation has been shown in several high-quality trials to be an effective treatment for motor fluctuations and dyskinesias in advanced PD, when compared to best medical therapy. The main targets for DBS are the subthalamic nucleus (STN) or the globus pallidus interna (GPi). STN DBS allows for greater reduction in medication but may be associated with worsening of non-motor symptoms and falls when compared to GPi. Stimulation of the GPi often has a beneficial direct effect on dyskinesia although with STN stimulation medications can often be lowered also resulting in less dyskinesia. For further discussion on the selection of DBS targets please see Williams *et al.*[5]

It is currently unclear which advanced intervention is the most effective as there have been no direct head-to-head studies. Treatment selection is typically based on several factors:

- Patient preference.
- Local availability/pathways—availability of advanced interventions may differ between centres. In addition, in the UK, NHS England requires patients to have trialled or be unsuitable for apomorphine infusion prior to considering intrajejunal levodopa.
- Intervention specific contraindications:
  - DBS—intracranial structural lesions or atrophy may increase the risk of a neurosurgical procedure, pre-existing balance impairment, and dysarthria may worsen with DBS.
  - Intrajejunal levodopa—significant obesity or previous abdominal surgery, pre-existing neuropathy
  - Apomorphine infusion—pre-existing significant dermatological disease, orthostatic hypotension, impulse control disorders
- Intervention specific benefits—DBS has a beneficial effect on tremor above that of the effects of levodopa and hence may be helpful in medication resistant tremor.

- Co-morbidities:
  - Significant concurrent medical disease, e.g. cardiac or respiratory complaints may render a surgical procedure higher risk.
  - Cognitive impairment may be exacerbated by DBS, particularly of the STN, and will make subsequent programming difficult. Whilst all the advanced interventions are avoided in dementia, patients with mild cognitive impairment may be better suited for intrajejunal intestinal infusion particularly if they have good carer support.
- Cost—DBS may have a higher upfront cost, but lower long-term cost.

For further discussion on patient selection for advanced interventions please consider reading Antonini *et al.* (2018).[6]

Non-motor symptoms

Non-motor symptoms are common in Parkinson's disease. These can often be severe and have a significant impact on a patient's quality of life. They can be present in advance of the motor symptoms in some patients, and tend to increase in severity and complexity as the disease progresses. These symptoms include dysautonomia (constipation, urinary dysfunction, and orthostatic hypotension), neuropsychiatric disturbance (cognitive dysfunction, depression, and psychosis), and disorders of sleep. We have described common management strategies for these symptoms. Further information with regards management of cognitive and genitourinary symptoms can be found in Chapters 14 (Dementia) and 20 (Uro-neurology), respectively.

Autonomic dysfunction

Autonomic dysfunction in Parkinson's spans the sympathetic, parasympathetic, and enteric nervous systems. Common symptoms include postural hypotension, constipation, urinary dysfunction, sexual dysfunction, sialorrhea, and hyperhidrosis.

Treatment of postural hypotension

First line: conservative measures include increased dietary salt, adequate fluid intake, and compression stockings.

Second line: Medication options include fludrocortisone, midodrine and pyridostigmine

Evidence base

Fludrocortisone and midodrine (see drug monographs Fludrocortisone, P. 580 and Midodrine, P. 646).

Treatment of constipation

First line: conservative measures include increasing physical exercise, drinking plenty of fluids, and increasing fibre intake.
Second line: Laxatives, e.g. macrogol.

Evidence base

Macrogol has been assessed in one RCT in PD patients (*n* = 57). There was a significant improvement in constipation in the macrogol group, compared to placebo.[7]

Treatment of sexual dysfunction

- *First line*: conservative measures such as pelvic floor exercises for women, medication review, and management of co-morbid anxiety can be helpful.
- *Second line*: Phosphodiesterase inhibitors, e.g. sildenafil, sex aids, dedicated sex and relationship clinics for patients with neurological disorders can also be helpful.

Evidence base

Sildenafil was assessed in one randomized, double-blind cross-over study for safety and efficacy in erectile dysfunction related to PD. Subjects (*n* = 20) treated with 25–100 mg of sildenafil 1h prior to sexual intercourse showed significant improvements in the ability to achieve and maintain an erection, compared to placebo.[8]

Treatment of sialorrhea

Management of sialorrhea can include conservative measures, oral therapies, and botulinum toxin injections. The main oral therapies in clinical practice are anticholinergics and these can lead to confusion individuals with Parkinson's disease, particularly if there is associated cognitive impairment. In these patients it would be reasonable to consider botulinum toxin injections if conservative measures fail.

- *First line*: conservative measures including regular fluid intake, head positioning, and queuing strategies.
- *Oral therapies*: e.g. glycopyrronium bromide and atropine drops.

Injection therapies: botulinum toxin injections into the salivary glands.

Evidence base

Glycopyrronium bromide (1 mg bd for 1 week) was assessed in a randomized, double-blind, placebo-controlled trial for drooling in PD (*n* = 23). It achieved >30% decrease in sialorrhea score, compared to placebo.[9] There have been no trials of hyoscine hydrobromide in PD-related sialorrhea. However, small, short-term studies have shown it to be effective. It is available as a transdermal patch and tablet.

BTX-A was assessed in a double-blind, randomized, placebo-controlled trial over 4 months, with an open-label extension study lasting 1 year. There was a sustained reduction in unstimulated salivary flow rate for at least 4 months post injections.[10]

Treatment of hyperhidrosis:

- *First line*: conservative measures including avoidance of triggers such as alcohol, heat, and spicy foods. Specialized clothing and absorbent pads for troublesome areas.

- *Localized treatments*: Anti-perspirants containing aluminium chloride. Glycopyrrolate solution, iontophoresis, and botulinum toxin
- *Generalized treatments*: Anticholinergics, e.g. glycopyrronium can be trialled but side effects such as confusion, hallucinations, and constipation are common in Parkinson's.

Evidence base

There are no RCTs that have evaluated the management of hyperhidrosis in Parkinson's disease. The above recommendations are based on common practice and management guidelines for primary hyperhidrosis.

Cognitive impairment and dementia

PD dementia (PDD) occurs in up to 50% of patients during the disease. Executive dysfunction and visuospatial deficits are prominent features, with relative preservation of memory, compared to Alzheimer's dementia. Visual hallucinations occurring earlier in the course of the disease increase the risk of developing cognitive impairment.

PDD and its management are discussed further in Chapter 14, Dementia.

Depression and anxiety

Depression and anxiety are present in up to 40% of individuals with PD. For some these symptoms only occur in the 'off' state. It is important to recognize this as symptoms only present in the 'off' state frequently improve when dopaminergic medications are optimized.

Treatment

No clear first-line agent has been identified to treat depression in PD. Commonly used agents include:

- SSRIs (fluoxetine, sertraline, citalopram, and paroxetine).
- SNRIs (venlafaxine and mirtazapine).
- TCAs (nortriptyline, desipramine, and amitriptyline)—beware side effect of confusion.
- DAs (pramipexole and ropinirole).

Evidence base

SSRIs are often used first-line, as they have a better side effect profile, minimizing the anticholinergic and pro-arrhythmogenic effects associated with TCAs. However, in patients with significant tremor and no cognitive deficit, the anticholinergic activity of TCAs may result in improvements in tremor, alongside improvement in mood.

Selective serotonin reuptake inhibitors (SSRIs)

Several small RCTs have assessed the efficacy of SSRIs in the management of PD-associated depression, with varying results. Citalopram, sertraline, paroxetine, and fluoxetine were reviewed in the most recent MDS evidence-based review, which concluded that they were possibly useful. This was based on the absence of placebo-controlled trials in the context of PD but established efficacy outside of PD.[11]

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs)

A randomized double-blind, placebo-controlled trial demonstrated a significant improvement in depression at 12 weeks with venlafaxine[12] and hence this is considered clinically useful by the MDS review.[11]

Cautions with SNRIs/SSRIs:

1. A small body of literature has highlighted the rare worsening of motor symptoms (up to 5%), particularly tremor with SSRIs. Therefore, introduction of these agents should be undertaken cautiously, with regular review of motor symptoms.
2. Combinations of SSRIs and MAO-B inhibitors pose the theoretical risk of serotonin syndrome. Caution should be taken if using both agents together (see drug monograph, Monoamine oxidase inhibitors, p. 413).

Dopamine agonists

A double-blind, placebo-controlled RCT (n = 287) of pramipexole (0.125–1.0 mg tds) showed a significant reduction in Beck Depression Inventory (BDI) scores, compared to placebo. The MDS evidence-based review concluded that pramipexole was efficacious and clinically useful in the treatment of PD-related depression.[13] Ropinirole has not been assessed by means of an RCT for this indication; however, a prospective cohort study (n = 44) showed significant improvement in depression and anxiety scores after 6 months.[14] Rotigotine has not been found to be efficacious for the management of depression.

Psychosis

Up to 40% of patients experience delusions and hallucinations. Risk factors include older age at onset, cognitive impairment, need for high doses of dopaminergic drugs, and rapid eye movement (REM) sleep behaviour disorder.

Management

1. *Review medications:* A reduction in antiparkinsonian therapy may alleviate psychotic symptoms. Consideration should be given to reduction or discontinuation of, in order of preference: anticholinergics, amantadine, COMT inhibitors, and DAs, reflecting the relative likelihood of each agent to cause or exacerbate psychosis. Levodopa dose reduction can also be considered as a last resort.
2. *Cholinesterase inhibitors:* Where psychotic symptoms are mild and occur in the context of cognitive impairment, agents such as donepezil and rivastigmine may improve symptoms.
3. *Antipsychotics:* Typical antipsychotics commonly aggravate motor symptoms in PD, because of their antidopaminergic activity. For this reason, atypical antipsychotics are preferred:
   - *First line*: quetiapine.
   - *Second line*: clozapine.

4. *Pimavanserin:* This is a serotonin 2A inverse agonist FDA approved for use in Parkinson's disease psychosis. It is not yet available in the UK. It is an effective antipsychotic agent which does not cause impairment in motor function compared to placebo and does not require intensive blood monitoring.

Evidence base

Although the available evidence for clozapine (several double-blind controlled trials) is stronger than for quetiapine (conflicting results from open-label and double-blind, placebo-controlled trials), quetiapine is often used in preference because of its more favourable side effect profile and easier monitoring schedule. Clozapine is estimated to cause neutropaenia in 3% of patients and agranulocytosis in 1% necessitating ongoing monthly blood monitoring.[11]

In a double-blind randomized controlled trial, Pimavanserin demonstrated a 37% improvement in psychotic symptoms without a deterioration in motor function.[15]

Sleep disorders

Sleep disorders are common in Parkinson's disease and include REM sleep behaviour disorder (RBD), insomnia, and excessive daytime sleepiness. Insomnia and RBD are discussed separately in Chapter 17, Sleep disorders.

Excessive daytime sleepiness

Excessive daytime sleepiness is a common non-motor feature of PD. It may result from the disease process itself, associated co-morbidities (e.g. obstructive sleep apnoea) or because of dopaminergic therapy. Sudden-onset sleep or 'sleep attacks' are an infrequent, but important, side effect of dopaminergic therapy and Non-ergot-based dopamine agonists, p. 395) . Both somnolence and sudden onset of sleep will impair the patient's quality of life and impact on their ability to drive.

Treatment

1. Lifestyle interventions: assess sleep hygiene and provide advice to ensure adequate sleep.
2. Modafinil.

Evidence base

Several RCTs have investigated the use of modafinil (200–400 mg/day) for excessive daytime sleepiness in PD. Only one showed a significant difference from placebo. No long-term efficacy or safety data are available, as no study lasted >4 weeks. The MDS evidence-based review emphasizes that modafinil for this indication remains under review and that larger, high-quality studies are needed.[11]

Parkinson's plus syndromes

Parkinson's plus syndromes, also known as atypical parkinsonism are a group of progressive neurodegenerative disorders. They often feature parkinsonism in association with a number of other symptoms and signs. Unfortunately, they often progress at a faster rate than idiopathic Parkinson's disease and patients typically only have a limited response to dopaminergic therapies. The following section details the management of multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.

Dementia with Lewy bodies is often included in this category. It is a syndrome characterized by a triad of fluctuating cognition, recurrent visual hallucinations, and spontaneous motor features of parkinsonism. Dementia must precede or accompany the spontaneous onset of parkinsonism, to differentiate this disease entity from PDD. PDD manifests >1 year after the typical motor symptoms of PD.

DLB and its management are discussed further in Chapter 14, Dementia.

Multiple system atrophy (MSA)

MSA is a rare neurodegenerative disorder, characterized by the combination of parkinsonism, dysautonomia, cerebellar dysfunction, and corticospinal degeneration. It has been estimated to occur in 3 in 100 000 people aged over 50, with an average age of onset of 56. Both men and women are affected equally. Symmetrical extrapyramidal signs, rapid deterioration of mobility with early falls, cerebellar signs, and early and prominent dysautonomia may help distinguish it from idiopathic PD. Diagnosis is based on clinical findings, poor response to levodopa, and supported by neuroimaging, such as abnormal dopamine transporter scan (DaTSCAN) and characteristic MRI findings.

Treatment

Like PD, there are currently no curative or disease-modifying treatments for MSA, and therapy is symptomatic.

1. *Parkinsonism:*
   - *First line*: a trial of levodopa (up to 1000 mg/day for 3 months). This can also help differentiate MSA from idiopathic PD. Classically, MSA is resistant to dopaminergic therapy, although 30% of patients may experience a transient improvement. Worsening postural hypotension, dyskinesias (in particular facial, or cervical dystonia), nausea, and vomiting may limit its use.
   - *Second line*: amantadine and DAs are sometimes used.
2. *Autonomic dysfunction:*
   - (See non-motor Parkinson's disease symptoms p. 177):

Evidence base

1. *Levodopa:* there are no controlled trials of levodopa for the treatment of MSA. Case series suggest ~30% of patients exhibit some benefit.[16] This is usually not sustained, and most patients experience deterioration in their

symptoms after a few years. Some patients report subjective benefit from levodopa therapy, without objective improvement in motor examination. Levodopa is less likely to cause psychiatric side effects and motor fluctuations in MSA than in PD, but dyskinesias may still occur.

2. *DAs:* there have been no controlled trials of DAs in MSA. Due to their increased side effect profile, compared to levodopa, they are not generally used.

3. *Amantadine:* a double-blind, placebo-controlled trial showed no benefit of amantadine in MSA. However, 5% of patients in an older series showed a 'good or excellent response', as rated by subjective assessment of the patient, or their family or clinician.[17]

4. *SSRIs:* a double-blind, placebo-controlled trial investigated the use of paroxetine (30 mg tds for 2 weeks) and concluded that there was a small, but statistically significant, improvement in motor symptoms during treatment.[18]

Progressive supranuclear palsy (PSP)

PSP is the commonest of the atypical parkinsonian syndromes, affecting up to 6.4 per 100 000 people, with an average age of onset at 62 years. Patients exhibit early gait disturbance with falls and significant axial rigidity, dysarthria, pseudobulbar palsy, and a characteristic eye movement abnormality (initially slowing of vertical > horizontal saccadic velocities, with progression to complete supranuclear gaze palsy). Insomnia and frontal cognitive abnormalities are common, but RBD is not.

Treatment

There are no curative or disease-modifying treatments for PSP, and therapies are symptomatic. As with other atypical parkinsonian syndromes, PSP is generally not responsive to levodopa, although a proportion of patients experience transient benefit.

- *First line*: consider a levodopa trial (up to 1000 mg/day for 3 months).
- *Second line*: amantadine.

Evidence base

There is a lack of clinical trial evidence of the efficacy of levodopa in PSP. Small retrospective series have reported temporary benefits in up to 54% of patients, with doses as high as 9000 mg/day. 'Modest improvement' was noted in four out of 12 patients in a series of post-mortem confirmed cases. Visual hallucinations are a common side effect of levodopa use in PSP.[19] There is a lack of clinical trial evidence for the efficacy of amantadine in PSP. Small retrospective series have noted transient therapeutic benefit in up to 29% of patients.[20]

Corticobasal degeneration

Corticobasal degeneration (CBD) is a progressive neurodegenerative disorder, characterized by asymmetrical onset of rigidity, apraxia, tremor, stimulus-sensitive myoclonus, and dystonia. Patients often complain of symptoms initially affecting one limb and may experience the alien limb phenomenon. Sensory symptoms are common, including significant pain. Cognitive and behavioural abnormalities are an important feature and often precede motor symptoms. The condition has been estimated to occur in 5–7 in 100 000 and has an average age of onset of 63.

Treatment

There are no curative or disease-modifying treatments for CBD. Management is with symptomatic treatment.

Parkinsonism:

- *First line*: trial of levodopa (up to 1000 mg/day for 3 months). A lack of response or a short-lived response is typical.

Myoclonus:

- Clonazepam, sodium valproate, piracetam, or levetiracetam.

Evidence base

There are no RCTs investigating the efficacy of treatments used in CBD. Small retrospective case series note transient mild to moderate improvement in parkinsonism with levodopa. Dyskinesias are a reported side effect.

Drugs to avoid in parkinsonism

Several medications used in everyday clinical practice have the potential to worsen the symptoms of PD.

Drug-induced parkinsonism is the second commonest cause of an akinetic rigid syndrome and is often the result of treatment with antidopaminergic medications (e.g. antipsychotics, antiemetics). Classically, drug-induced parkinsonism is thought to be reversible on stopping the offending agent. However, drugs may un-mask an underlying neurodegenerative parkinsonism. A review of medications in all patients presenting with parkinsonism is important to ensure causative or exacerbating agents are stopped.

Please see box 11.1 commonly used agents which should be avoided or used with caution in patients with parkinsonism.

Drugs which can exacerbate parkinsonism

- Antiemetics:
  - metoclopramide.
  - prochlorperazine.
- Antihistamines:
  - promethazine.
  - alimemazine.
- Anticonvulsants
  - sodium valproate
- Antipsychotics:
  - chlorpromazine.
  - clozapine.*

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* Medications frequently used in PD patients.

  - flupentixol.
  - fluphenazine.
  - haloperidol.
  - olanzapine.
  - pimozide.
  - quetiapine.*
  - risperidone.
  - thioridazine.
  - trifluoperazine.
  - zuclopenthixol.
- Calcium channel blockers:
  - cinnarizine
  - flunarizine
- Dopamine degradation
  - tetrabenazine
- Mood stabilizers
  - lithium

Impulse control disorders

ICDs are pathological behaviours thought to be the result of altered reward or incentive mechanisms, likened to addiction. They are a group of disorders characterized by excessive or compulsive repetition of pleasurable behaviours typically gambling, hypersexuality, compulsive buying and binge eating. They are rare in the general population but are far more common in patients with Parkinson's exposed to dopaminergic treatments, particularly DAs.

Management of impulse control disorders

Recognition of ICDs is often difficult, due to a patient's lack of insight into pathological behaviours and their association with dopaminergic therapy, or embarrassment. Patients and families should be made aware of common ICDs and be advised to alert their physician if they occur.

Following diagnosis, management should be undertaken in a multidisciplinary setting, with involvement of a PD nurse specialist and psychological support services.

- Dopaminergic therapy should be gradually reduced, with close monitoring of motor performance. Withdrawal symptoms may occur if the dose reduction is too rapid.
- Where possible, DAs should be discontinued, and levodopa or alternative therapies, e.g. DBS, used in their place.
- For some patients, changing dopaminergic agonists may be effective. Theoretically DAs with higher D3 receptor affinity are more likely to induce ICDs (e.g. pramipexole > ropinirole). However, any difference clinically between these two agents was not apparent in the DOMINION study.
- Antidepressants (e.g. SSRIs) can help pathological gambling.
- Atypical antipsychotics (e.g. quetiapine, clozapine) may be of benefit for hypersexuality.

Evidence base

1. There have been very few robust studies on pharmacological treatment of ICDs in PD. Case reports and case series have reported improvement in ICDs following reduction and/or discontinuation of DA therapy, with suggestion of improvement in some patients when switching from agents with relatively high D3 affinity.
2. The DOMINION study was a large cross-sectional study investigating ICDs in PD. An ICD was identified in 13.6% of 3090 patients. They were significantly more common in patients taking dopamine agonists (17.1% vs. 6.9%; OR 2.72). There was no significant difference in patients on pramipexole or ropinirole.[21]
3. Treatment of pathological gambling with SSRIs, including fluvoxamine ($n = 10$) and paroxetine ($n = 45$), has been assessed in small placebo-controlled RCTs. Short-term benefits were shown by both agents. These studies were not specific for PD-related ICDs.[22]
4. Case reports have suggested a role for atypical antipsychotic treatment in cases of hypersexuality.

Dopamine agonist withdrawal syndrome

DAWS is a constellation of autonomic and neuropsychiatric symptoms that can occur following the reduction and discontinuation of DA treatment. Autonomic symptoms include postural dizziness and sweating, and neuropsychiatric symptoms include depression, anxiety, fatigue, and insomnia.

Management of dopamine agonist withdrawal syndrome

Gradual reduction of DA will reduce the likelihood of DAWS. Awareness and early recognition are important, and the substitution of alternative dopaminergic therapy is often necessary. There are several case reports describing successful use of off-licence drugs (e.g. apomorphine). Published series indicate that DAWS resolves within 6 months in most cases. In a small proportion of patients, the DA cannot be completely discontinued. Patients and carers should be informed about the possibility of DAWS before starting DA treatment.

Evidence base

There are no RCTs investigating the management of this condition; thus, treatment recommendations are based on case reports and expert consensus.

Neuroleptic malignant syndrome/ Parkinson's hyperpyrexia syndrome

NMS is a life-threatening neurological emergency. NMS or an NMS-like syndrome may develop in the setting of PD. This is termed Parkinson's hyperpyrexia syndrome. Both syndromes typically result from a reduction of dopaminergic activity either via the use of antidopaminergic agents, or in the context of PD more commonly with dose reduction or change in dopaminergic agent. The syndrome consists of fever, rigidity, change in mental status, and dysautonomia with fluctuating BP, tachycardia, sweating, and urinary incontinence. It is important to recognize and treat early as systemic complications including thromboembolism, aspiration pneumonia, and renal failure can occur. In severe cases, patients may continue to deteriorate in spite of dopaminergic therapies and require intensive care support.

Management of neuroleptic malignant syndrome/ Parkinson's hyperpyrexia syndrome

Management is primarily supportive, aiming to reverse any changes in dopaminergic drugs, including terminating the use of antidopaminergic medications where possible.

In moderate to severe PHS:

1. Medication changes are reversed, and levodopa is typically started or increased.
2. Dopamine agonists can be added if an oral route is not available:
    - Rotigotine patches
    - Subcutaneous apomorphine infusion

Severe PHS

3. bromocriptine can be trialled, e.g. 2.5 mg every 6–8 h PO or via nasogastric tube, then titrated over 48 h up to 30–40 mg/day.
4. Muscle relaxants can be used for severe rigidity:
    - dantrolene: 25 mg every 8 h PO or 1–2.5 mg/kg IV (can be repeated to a maximum dose of 10 mg/kg/day).

Severely ill patients may require intubation and ventilation in an intensive care setting. Most cases resolve within 2 weeks, with little residual deficit. Poorer outcomes are noted in those with complicating renal failure or a background history of drug or alcohol abuse.

Evidence base

There are no RCTs investigating the management of NMS/PHS, and treatment recommendations are based on published reports and expert consensus.

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Chapter 13

Hyperkinetic movement disorders

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Introduction

Hyperkinetic movement disorders are characterized by an excess of movement. They are classified by clinical phenotype and include chorea, dystonia, myoclonus, tics, and tremor. Treatment options have rapidly increased recently, and there are now a wide variety of both pharmacological and neurosurgical approaches to aid long-term management of these conditions.

This chapter will discuss the clinical features, management, and evidence base for the treatment of the various hyperkinetic movement disorders, focusing on those amenable to symptomatic treatment. Each hyperkinetic movement may have multiple aetiologies; however, we have focused on symptomatic treatment of the specific movement as disease specific therapies are further discussed in their individual chapters, e.g. multiple sclerosis causing Holmes tremor would be discussed in Chapter 6, Multiple sclerosis and related disorders.

Tremor

Tremor is defined as an involuntary, rhythmic oscillatory movement of a body part. It is classified based on the clinical features and the underlying aetiology. Tremors can be divided by the presence or absence of characteristic features, including whether they occur at rest (e.g. parkinsonian tremor) or on action (postural, kinetic, and intention tremors).[1]

1. *Resting tremor*: this is most often seen with PD and parkinsonism. It is present at rest, is terminated on action, and most commonly affects the arms, legs, and chin.
2. *Postural tremor*: this refers to a tremor present when a body part maintains a position against gravity. The underlying causes include enhanced physiological tremor, essential tremor (ET), dystonic tremor, or PD. It most often affects the arms, head, and neck.
3. *Kinetic tremor*: this refers to a tremor present on movement of a body part. The commonest cause is ET.
4. *Intention tremor*: this refers to a tremor whose amplitude increases, as the body part nears its target. It is often a sign of cerebellar pathology but may also be present in ET.

The effect of tremor on function will depend upon its amplitude and the limbs involved. Treatment options depend on the type of tremor, the likely underlying pathophysiology, the level of functional disability, and the patient's tolerance to medication.

Essential tremor

ET is characterized by an 8–10 Hz tremor, which commonly affects the hands and arms. Males and females are equally affected. Alcohol consumption can often lead to transient resolution of ET, with rebound worsening of tremor described when the effects wear off. Those that receive treatment often struggle with the side effects of commonly used agents.

Treatment

- *First line*: propranolol or primidone.
- *Second line*: topiramate.

- *Other*: benzodiazepines (e.g. clonazepam), clozapine, gabapentin, olanzapine, zonisamide, or botulinum toxin injections.
- *Surgical*: Deep brain stimulation (DBS) or ablation of the ventral intermediate (VIM) nucleus of the thalamus (including MRI-guided focused ultrasound), contralateral to the most severely affected limb. Bilateral thalamotomy is not routinely performed, due to the high risk of speech disturbance and other side effects.

Evidence base

First-line therapies:

Propranolol and primidone have the strongest evidence base for use in the management of ET. Multiple RCTs have demonstrated their effectiveness. Both agents reduce tremor by ~50%, as measured by accelerometry. As a result, the AAN and MDS have given both these agents the highest level of recommendation of efficacy.[2,3] Primidone is usually used second line to β-blockers, due to its broader side effect profile—sedation and vomiting are the commonest dose-limiting side effects, although depression, as well as cognitive and behavioural disturbances typical of barbiturates, can also be a problem. If patients have a history of asthma or experience bronchospasm with propranolol, a selective β1-adrenergic receptor blocker can be trialled such as atenolol. RCTs, including comparative studies with propranolol, have shown that atenolol is effective in the management of ET, but there is no evidence that it is more effective than propranolol. Sotalol, nadolol, and metoprolol have also demonstrated efficacy in small studies. The 2019 MDS evidence-based review[2] and 2011 AAN evidence-based guideline update are summarized below.[3]

Other anti-epileptics:

Four trials have compared topiramate to placebo, demonstrating a significant improvement in functional disability but with an increased rate of adverse effects, resulting in 30–50% of patients dropping out. The mean effective dose was 215–333 mg/day.

A single small study of 20 people suggested that zonisamide may be effective in the treatment of ET. Gabapentin may improve ET when used as a monotherapy but results from trials have been conflicting.

Levetiracetam and pregabalin have not been reliably shown to be effective.

Antipsychotics:

Olanzapine at doses of ~20 mg/day has been compared to propranolol at doses of 120 mg/day in the context of one small RCT and no significant difference was found between the two agents. 40% of patients felt their tremor improved completely at 1 month.

In one small open-label trial of clozapine in 12 patients, 7 patients had a significant improvement in tremor at doses between 18 and 36 mg.

Botulinum toxin injections:

RCTs of botulinum toxin have shown that, when wrist extensors and flexors are treated, a 57–68% improvement in postural hand tremor can be expected. The degree of improvement in the kinetic tremor may be less. However, significant arm weakness occurred in 70% of patients at higher doses. Smaller subsequent trials have suggested that the degree of weakness and overall outcome can be improved by using lower doses, an individualized approach, predominantly injecting the forearm flexors, and by using electromyography.

Holmes' tremor

The Holmes' (also known as midbrain, thalamic, or rubral tremor, depending on the lesion site) is typically a symptomatic tremor associated with an underlying lesion, (or more commonly multiple lesions) in the brainstem, thalamus, or cerebellum. It is most often seen with vascular or inflammatory (e.g. MS) lesions, it can also be seen after traumatic brain injury. The tremor is typically low frequency (3–5 Hz) and has both rest and intention components. A postural tremor may also be present. It is thought to result from both disruption of nigrostriatal neurons and either the cerebello-thalamo-cortical or dentato-rubral-olivary pathways. Other signs of brainstem involvement are often present, including eye movement abnormalities, hemiparesis, and ataxia.

Treatment

Holmes' tremors can be very disabling and are not uncommonly refractory to medications. There is only case series-level evidence for the use of most pharmacological agents.[4] Levodopa is one of the more commonly used agents (at doses between 300–1000 mg/ day) and may improve tremor control (rest, postural and kinetic components) in up to 50% of patients and hence should be considered first. Other agents including clonazepam, trihexyphenidyl, pregabalin, primidone, propranolol, *valproate and topiramate have been reported to be effective in a few patients. Botulinum toxin has also been reported to reduce tremor in some patients.

Surgical treatments have gained popularity. Thalamotomy and DBS of the contralateral ventral intermediate nucleus (Vim) have led to positive results in small case series. However, patients need to be carefully selected as the overall contribution of tremor to functional impairment may be minimal. Depending on the underlying lesion there may be co-existent ataxia and/or spasticity, and this frequently persists and may even worsen with surgical intervention. The proximal tremor is also harder to treat when compared to the distal component. Due to the reversibility and ability to adjust stimulation with symptom severity, DBS is preferred; yet robust comparative evidence between surgical techniques is lacking.

Orthostatic tremor

Orthostatic tremor refers to a group of conditions characterized by a tremor, predominantly of the legs on standing. It can be classified in terms of the tremor frequency or whether it is a primary or secondary disorder.

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If secondary it typically occurs in the context of an underling, usually neurodegenerative, disease. Primary orthostatic tremor refers to a high frequency 13–18 Hz tremor. Orthostatic tremor of <13 Hz, is labelled variably slow orthostatic tremor or pseudo-orthostatic tremor and is more likely to be associated with an underlying neurological condition.

The choice of treatment is guided by clinical experience, there are no RCTs. Clonazepam and gabapentin are typically used first line and can be moderately effective, although their side effects can be dose limiting. Levodopa and other dopamine-based medications can be effective, particularly in pseudo-orthostatic tremor, where there is often underlying parkinsonism. Primidone, propranolol, perampanel and *valproate have also been tried although only in the form of small case series. For refractory cases deep brain stimulation of the VIM nucleus of the thalamus has been helpful in a few patients.

Occupational and physiotherapy review are often important aspects of treatment. There is further information and patient education on www.orthostatictremor.org.

Dystonia

Dystonia is characterized by sustained muscle contraction of one or more muscle groups, resulting in abnormal posturing, with or without abnormal movements of the affected limbs. It can be classified based on aetiology, age at onset, and by the areas of the body affected (focal: one body part; segmental: at least two adjoining body parts; multifocal: at least two non-contiguous body parts; haemidystonia: unilateral arm, leg, and face involvement; and generalized: involving the trunk and two other limbs). Additional features include '*gestes antagonistes*' also called a 'sensory trick' wherein touching an affected body part may result in temporary resolution of the symptoms.

Treatment

The treatment of dystonia is predominantly symptomatic, with medications aimed at promoting muscle relaxation. Only rarely are drugs used which target the underlying condition, e.g. dopa-responsive dystonia (DRD). Pharmacological treatments can be divided into two main groups:

1. Botulinum toxin can provide significant symptom relief in isolated muscle groups and is very effective in focal forms of dystonia or generalized forms where symptoms from one or a few muscle groups predominate.
2. Systemic treatments may be required in more widespread forms of the condition or instances where botulinum toxin is either ineffective or not tolerated in the treatment of focal dystonia. Due to the nature of these treatments and their potential for systemic side effects, trials of treatment should be used to establish which therapies can provide maximal symptom relief, with minimal adverse effects.

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In addition to drug treatment, can be helpful. Targeted DBS and ablative surgeries of the globus pallidus interna are also becoming increasingly popular. They can be highly effective, even in patients with dystonia refractory to pharmacological interventions, and often mean that systemic treatments for dystonia can be stopped or significantly reduced, avoiding, or minimizing their potential side effects.

Focal

Focal dystonia affects one body part and is more commonly seen in adults. The commonest focal dystonia is cervical dystonia, e.g. torticollis; other forms include blepharospasm, oromandibular, laryngeal and task-specific dystonia.

Treatment

- *First line*: botulinum toxin.
- *Second line*: oral agents or surgical interventions, e.g., DBS or selective denervation (see Generalized, Dystonia, below).

Evidence base

Botulinum toxin is highly effective in the management of focal dystonia. An estimated 90% of patients with blepharospasm will demonstrate clear symptomatic improvement with treatment.[5] Further RCTs have also confirmed significant improvements when used in the management of cervical, oromandibular, limb, and laryngeal dystonias. Where treatment fails, i.e. if antibodies form, then different toxins including type B formulations can be trialled. If these fail then pharmacological agents used for generalized dystonia are often trialled, although side effects are more common in older patients. DBS or peripheral nerve lesions, e.g. rhizotomy for cervical dystonia or recurrent laryngeal nerve crush for laryngeal dystonia are potential options for severe toxin-refractory cases.

Generalized

Generalized dystonias encompass a wide group of conditions, with a diverse aetiology, including genetic disorders, brain injury (e.g., at birth or stroke), infection, drug-related, or idiopathic (often believed to be a genetic condition where a mutation has not yet been found). Early-onset generalized dystonias usually present in late childhood, often beginning as a focal limb dystonia and then generalizing. Where a definitive aetiology has not been identified in early-onset dystonia, a diagnostic trial of levodopa should be undertaken (see Dopa-responsive dystonia, p. 193).

Treatment

Oral medication is often preferred to botulinum toxin. A combination of agents may be required for optimum symptom control.

- *First line*:
  - diagnostic levodopa trial (DRD).
  - trihexyphenidyl (side effects particularly common in the elderly).
- *Second line/adjuncts*:
  - baclofen (PO/intrathecal) (may be used as monotherapy, as tolerated better in the elderly than trihexyphenidyl).
  - benzodiazepines (e.g. clonazepam).

  - botulinum toxin if symptoms from one or a few muscles predominate.
  - tetrabenazine.
  - zonisamide (myoclonus dystonia).
  - Triple therapy with an anticholinergic, tetrabenazine, and a dopamine antagonist (atypical antipsychotics such as clozapine) may be beneficial in severe generalized dystonia.
- Surgery: localized ablation or DBS.

Evidence base

- Due to the variable presentation of DRD, a trial of levodopa for 4 weeks is often undertaken. Following this, symptomatic treatment may be started with trihexyphenidyl, the anticholinergic with the greatest evidence base for the treatment of dystonia. Sustained benefit was noted after 2 years in 41% of patients treated in one RCT. PO baclofen may improve dystonia-related gait disorder, with intrathecal preparations being of benefit for significant lower limb spasticity. Benzodiazepines such as clonazepam may be helpful in jerky dystonia or myoclonus dystonia but should only be used for short periods due to concerns about tolerance and dependence.
- In one RCT of 23 people with myoclonus dystonia, use of zonisamide at 300 mg/day resulted in a significant improvement in myoclonus, functional status, and to a lesser extent dystonia when compared to placebo.[6]
- *Surgery*: surgical options can be broadly categorized into lesional surgery (pallidotomy and thalamotomy) and DBS. Due to the permanent nature of its potential side effects, lesional therapy is now less commonly used and reserved for instances where DBS is not suitable or where prior use has resulted in complications. It is used predominantly where there is a lack of sufficient response to oral agents or botulinum toxin, particularly in those with primary dystonia. The globus pallidus internus (GPi) has been shown to be the optimal target for lead placement. The results from RCTs suggest improvement can be expected in 40–60% of patients.[7,8]

Dopa-responsive dystonia

DRD is a rare genetic dystonia. It typically presents as a childhood-onset progressive dystonic syndrome, which shows a significant response to low-dose levodopa treatment. Symptoms usually begin in the legs and become generalized, with many later developing parkinsonism. Often symptoms are improved after sleep. DRD may also rarely present in adulthood, and this can be with predominant parkinsonism rather than dystonia.

Treatment

- *First line*: levodopa.

Evidence base

The characteristic feature of DRD is the dramatic and sustained effect of low-dose levodopa treatment. Several series have highlighted that most

DRD patients usually require around 300 mg/day of levodopa. Rarely, doses from 600 to 1000 mg/day are required. Patients have been shown to be stable on low-dose levodopa for up to 22 years.[9,10] Motor complications, as seen with levodopa treatment in PD, rarely occur in DRD (<20% at a mean disease duration of ~30 years (range 5–54 years)). Those who develop 'wearing off' phenomena or dyskinesias may represent childhood-onset parkinsonism.

Tics and Tourette's syndrome

Tics are sudden, brief, 'unvoluntary' movements (motor tics) or vocalizations (phonic tics). An important distinction between tics and the other hyperkinetic movements (e.g. myoclonus and dystonia) is the ability of patients to suppress them, during which time patients often describe a rising urge or an internal unrest. This may be followed by a rebound exaggeration of their tics.

Tourette's syndrome

Tourette's syndrome (TS) is a chronic neurodevelopmental disorder, characterized by the presence of:

1. Multiple motor and one or more vocal tics.
2. Onset before the age of 18.
3. Tics for at least 1 year.

The decision to commence treatment of tics or TS should be made based on the degree to which manifestations of these conditions intrude into a patient's life. Tics often warrant treatment if they involve self-injurious behaviour or are significantly socially or academically disruptive. Malignant Tourette's describes patients where their tics have led to repeat hospital admissions typically due to the severity of the consequent injuries.

Patients and their families should be counselled on the realistic outcomes of treatment and the potential side effects of medications. The natural history of Tourette's and tics are that they wax and wane depending on concurrent stressors and co-morbidities, typically becoming more manageable with increasing age.

Often mild tics do not require pharmacological treatment, and reassurance may be all that is required. If treatment is considered, psychological support and behavioural therapy, such as habit reversal therapy, should be offered alongside medications. It is also critically important to treat co-morbid obsessive compulsive disorder (OCD), anxiety, and depression, which may be more distressing to the patient than the tics. Often effective treatment of these co-morbidities will significantly improve tics.

Treatment

- A2-adrenergic agonists (clonidine or guanfacine) particularly if co-morbid attention-deficit/hyperactivity disorder (ADHD).

- Antipsychotics (atypical: aripiprazole or risperidone; typical: haloperidol, pimozide, or sulpiride).
- Tetrabenazine and other dopamine-depleting agents available in the USA, not UK: deutetrabenazine and valbenazine.
- Other: benzodiazepines (e.g. clonazepam), topiramate (particularly if there is co-morbid obesity), or tetrahydrocannabinol (THC) products.
- Adjunct: botulinum toxin (focal motor or simple vocal tics, particularly if the patients are at risk of injury, e.g. cervical 'whiplash' tics, which can result in secondary myelopathy and repetitive movements around a joint which can lead to recurrent dislocations).
- Surgical: DBS and stereotactic brain surgery can be considered for severe cases.

Evidence base

Pharmacological treatments are selected and trialled based on tic severity, patient co-morbidity, and the known side effect profile of the commonly used agents. Cross-comparator studies of various agents are not available.

Antipsychotics

A meta-analysis of RCTs established that antipsychotics are probably the most effective agents for the management of tic disorders—the standardized mean difference (SMD), compared to placebo, is 0.58 (95% CI 0.36–0.80). However, due to their side effect profile (extrapyramidal symptoms, risk of long QT syndrome and weight gain), they are reserved for those with moderate to severe tics.[11] There is no clear evidence to suggest that one agent is more effective than another although their side effect profiles can vary and should be taken into consideration. The 2019 AAN practice guidelines highlight that the evidence base is strongest for haloperidol, risperidone, aripiprazole, and tiapride.[12] Tardive complications are more common with haloperidol, olanzapine, and pimozide, whilst the risk of weight gain and hypersomnolence are higher with aripiprazole and risperidone.

α2-agonists

Studies investigating the use of α2-agonists suggest that patients with co-morbid ADHD are most likely to benefit from treatment, as trials that excluded patients with ADHD demonstrated only a small, non-significant benefit.[12]

Dopamine depleting agents

Tetrabenazine and the newer agents are increasingly being used off-label in the treatment of Tourette's. There are no double-blind RCTs looking at tetrabenazine in this context, but it is frequently used for this indication.[12] Phase 2 trials looking at valbenazine and deutetrabenazine have not provided clear results, which may be due to the high placebo response rate in these trials. Phase 3 trials are ongoing. The newer agents likely have a better side effect profile in terms of parkinsonism, depression, and drowsiness.

Clonazepam

There are open-label studies in adults where clonazepam has shown some benefits in the treatment of tics. Due to development of tolerance, sedation, and memory problems, long-term use of these agents is limited although they may be helpful for short-term crises.

Topiramate

One small RCT ($n = 29$) looked at the use of topiramate in Tourette's and identified a significant improvement in the total tic score over 70 days. Mean doses were 118 mg/day.[13]

Tetrahydrocannabinol (THC)

Two small double-blind, cross-over, RCTs have suggested that THC may improve tic severity. However, a Cochrane review concluded that the trials were too small and too short to provide significant evidence of efficacy.[14]

Botulinum toxin injections

Botulinum toxin has been used in several case series and one small RCT. The RCT was published in 2001 and demonstrated a significant 40% reduction in tics/min vs. 6% with placebo ($p = 0.004$) and a significant decrease in the associated urge.[15] Paradoxically a small percentage felt that the urge increased, and they were unable to perform the movement that typically relieved it. Injection of the vocal cords for vocal tics has also been trialled, open-label case series suggest a benefit. Use of the toxin comes with significant risks of weakness and in the context of vocal tics, hypophonia. It is probably most useful in severe focal tics, e.g. whiplash tics where there is a risk of severe secondary disability.

Chorea, ballism, and athetosis

Chorea is a disorder characterized by involuntary, irregular, and random movements that appear to flow from one muscle to the next. It may affect any body part but is most commonly, generalized. Ballism is more explosive and proximal in nature. When affecting one side, it is termed hemiballism or hemiballismus, and is traditionally associated with, but not limited to, a lesion of the contralateral subthalamic nucleus (STN). Athetosis often accompanies chorea and is a slower writhing and twisting movement that presents distally. When chorea is thought to occur secondary to the used of anti-dopaminergic therapy it is termed tardive dyskinesia. These and other tardive syndromes are discussed further in Chapter 21, Drugs causing neurological disease.

Treatment

In some cases, the underlying disorder may be treated (e.g. systemic lupus erythramotosis (SLE), rheumatic fever, thyrotoxicosis, polycythaemia), however often treatment is aimed at symptom relief through reduction in central dopaminergic activity. Often patients are unaware of the extent or the presence of athetosis or chorea. Indications to start treatment may include the presence of physical injury, gait instability, interference with daily activities, stigma, and sleep disturbance. Medication trials should be undertaken to achieve the best symptomatic control with minimal side effects. The specific therapies used may differ depending on the underlying disease, where age or co-morbid psychiatric disorders mean that the clinician will often prefer to trial one drug preferentially, out of several potential options.

The following pages discuss the management of the common causes of chorea: Huntington's disease (HD), Sydenham's chorea, and tardive dyskinesia. If chorea occurs outside of these contexts, then a dopamine-depleting agent or antipsychotic can be trialled in a similar fashion to that used for HD, although the medications are not specifically licensed for this, and the evidence base is limited.

Huntington's disease

HD is the most common cause of inherited chorea. It manifests as dementia, psychiatric disturbance, and a mixed movement disorder (dystonia, parkinsonism, and chorea).

Treatment of chorea

- *First line*: tetrabenazine, deutetrabenazine, or antipsychotics.
- *Second line*: amantadine or riluzole.

Treatment of rigidity

This is common, particularly in the Westphal variant of HD and can respond to levodopa therapy if it is not felt to be medication related. It is typically used at lower doses than idiopathic PD.

Treatment of cognitive impairment

Small studies, including 2 RCTs have looked at the efficacy of donepezil, rivastigmine, and memantine but have not identified a clear benefit on cognition in HD.

Treatment of mood/psychotic disorders

Management of mood and behavioural disturbances that commonly occur is important. Treatment is typically with a combination of antidepressants, antipsychotics, and anxiolytics, in addition to counselling. Care should be taken that focusing on the motor symptoms does not exacerbate the underlying mood disorder, which is often more disabling for the patient. Patients and their carers should also be offered psychological support.

Evidence base

Dopamine depleting drugs

Tetrabenazine will reduce chorea in ~80% of HD patients.[16] It is the only drug that has been approved in the UK for HD-related chorea. Side effects of parkinsonism (more likely at high doses >100 mg), drowsiness, and depression (which can be severe and associated with suicidal ideation) are important and common (present in over 80% in some studies). They are reversible with treatment withdrawal. Active psychiatric disease or depression are a contraindication for use. Here an atypical antipsychotic, such as risperidone, olanzapine, or clozapine, may be more appropriate. Classical antipsychotics, such as haloperidol, are also effective but are associated with an increased risk of extrapyramidal side effects and are not typically used first line.[17,18] In the USA the FDA has also approved deutetrabenazine for the treatment of HD-associated chorea and there are studies in process looking at valbenazine for the same indication. There have been no head-to-head studies comparing tetrabenazine with deutetrabenazine but an unblinded cross-over trial and retrospective comparisons of the trials evaluating both agents suggest there isn't a significant variation in efficacy in the two agents.[19,20] The comparisons suggested that there were lower levels of depression and drug-induced parkinsonism with deutetrabenazine.

Other agents used for chorea

RCTs investigating the use of amantadine and riluzole for HD-related chorea have failed to demonstrate clear beneficial effects. Small RCTs have suggested that riluzole (50 mg bd) can provide a mild to moderate reduction in choreiform movement; however, this effect was lost when the results were re-analysed, excluding patients on antipsychotics. Larger and longer studies have not demonstrated beneficial or neuroprotective effects.[21] One RCT investigating the use of amantadine (100 mg tds for 2 weeks) demonstrated only subjective improvement in quality-of-life scores reported by patients, with no changes in objective measures of choreiform activity. Another RCT reported an 18% improvement in chorea with amantadine treatment, compared to 5% with placebo.[22] Based on these findings, the AAN suggests these agents may be considered as second-line agents in the treatment of HD chorea.[23]

Sydenham's chorea (St Vitus' dance)

Sydenham's chorea is an infrequent manifestation of rheumatic fever in children. The condition is usually self-limiting. In over 50% of patients, complete remission occurs in 2–6 months. However, a significant number of patients may have mild to moderate persistent symptoms after 2 years, and recurrence has been reported in up to 25% of patients. Where chorea is troublesome or there is a psychiatric disturbance, patients may benefit from an agent to reduce chorea:

Treatment of chorea

- *First line*: carbamazepine
- *Second line*: atypical antipsychotics or dopamine depleting agents, e.g. tetrabenazine, sodium valproate*

Treatment of chorea paralytica

- Corticosteroids, IVIg, or PLEX can be considered.

Antibiotics

- Typically, a treatment course of penicillin is given for 10 days to eradicate the streptococcus.
- Consequently, secondary prophylaxis with penicillin is recommended to prevent rheumatic heart disease (typically penicillin 250 mg BD) for 5 years or until age 21, whichever is longer. This may be extended if there is significant cardiac disease.

Evidence base

There have been no RCTs investigating the treatment of Sydenham's chorea. The evidence for pharmacological therapy is based on case reports and small, unblinded prospective studies without control arms. A study in 15 children found valproic acid (10–15 mg/kg/day) resulted in improvement in 13 children within 1 week. Carbamazepine (4–10 mg/kg/day) was also shown to have a beneficial effect in one small prospective study of nine children; the majority improved within 4 weeks. Carbamazepine and valproate have been compared in an unblinded prospective study ($n = 24$).[24] Both agents resulted in clinical improvement; however, no significant difference was noted in time to clinical improvement, time to complete remission, duration of therapy, or recurrence rates between the two drugs. Antipsychotics and tetrabenazine have also been demonstrated to work in similar small studies, although they probably have a more severe side effect profile than anti-epileptics.

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A small proportion of patients develop a severe form of the condition, refractory to traditional anti-chorea agents. In 'chorea paralytica' patients are unable to walk because of choreiform movements and hypotonia. Small case series have suggested that corticosteroids as oral tablets or as intravenous therapy, IVIg, and PLEX may improve the rate of recovery.

Myoclonus

Myoclonus is the sudden involuntary jerking of a muscle group, caused by the rapid contraction of agonist and antagonist muscles (positive myoclonus) or loss of tonic muscle tone (negative myoclonus, e.g. asterexis seen in hepatic encephalopathy).

The origin of myoclonus may be cortical, subcortical, spinal, or peripheral. Clinical features may help to differentiate one from the other.

- *Cortical myoclonus*: the commonest form; predominantly affects the face and distal limbs (arms > legs, reflecting sites of greatest cortical representation, as myoclonus is generated in the contralateral prefrontal cortex) and is often stimulus sensitive.
- *Subcortical/brainstem myoclonus*: this often affects multiple muscle groups and is frequently bilateral, affecting the axial or proximal muscles. Contractions are often of longer duration than those seen in cortical myoclonus and are frequently stimulus-sensitive (e.g. auditory).
- *Spinal myoclonus*: these are jerks of groups of muscles innervated by the same nerve root. They can be stimulus-sensitive and may occur during sleep as well as when awake.
- *Peripheral myoclonus*: caused by a lesion to a nerve, plexus, or root. One of the most common forms is hemifacial spasm. This is characterized by involuntary paroxysmal contractions of facial nerve innervated muscles. It is typically unilateral, although rarely occurs bilaterally (<5%) where muscular contractions on either side of the face are asynchronous. It is divided into primary and secondary forms. The primary form is thought to be related to pressure on the facial nerve by an aberrant posterior fossa artery. Spasm can also occur secondary to several aetiologies including multiple sclerosis, previous Bell's palsy, and compressive lesions.

Treatment

Any underlying medical condition should be treated first (e.g. liver, or renal disease resulting in a metabolic encephalopathy). In addition, medications known to cause myoclonus, e.g. those with serotonergic activity should be stopped where possible. Symptomatic treatment is achieved through increasing GABA-ergic neurotransmission. All treatments should be commenced at a low dose and gradually increased to achieve adequate control. Combination therapy is frequently required, with treatment often being only partly successful.

- Cortical myoclonus:
    - *First line*: levetiracetam or piracetam.
    - *Second line*: *sodium valproate, perampanel, primidone, or clonazepam.
- Subcortical and spinal myoclonus:
    - *First line*: clonazepam.
- Peripheral myoclonus (e.g. hemifacial spasm):
    - *First line*: botulinum toxin.
    - Oral medications such as carbamazepine, clonazepam, and baclofen can be trialled although side effects typically outweigh the usually mild benefits.
    - Surgical treatment of a compressive lesion e.g., a posterior fossa tumour in the case of hemifacial spasm may also be helpful.
- Drugs to avoid: carbamazepine, gabapentin, and phenytoin are known to exacerbate myoclonus and myoclonic epilepsy.

Evidence base

Cortical myoclonus

As cortical myoclonus is related to myoclonic epilepsy, antiepileptic agents are often the first drug of choice. There is little strong evidence for the treatment of myoclonus. Piracetam (2.4–16.8 g/day) has been shown in a small placebo-controlled, double-blind, cross-over trial of cortical myoclonus (n = 21, duration 14 days) to improve motor impairment, writing, and functional disability. It is well tolerated; however, large doses (up to 24 g/day) may be required for adequate control.[25] Levetiracetam (2–3 g/day), which is an analogue of piracetam, may be effective and is better tolerated with fewer side effects. Small observational studies and expert opinion highlight clonazepam (up to 15 mg/day) and sodium valproate (up to 1200–2000 mg/day) are also effective for cortical myoclonus. Standard antiepileptic medications do not appear to be effective in subcortical myoclonus. Clonazepam has been trialled in small studies and is used first line in subcortical myoclonus, based on expert opinion.[26]

Peripheral myoclonus

A systematic review of the literature published in 2015 found 5 RCTs looking at the utility of botulinum toxin in the management of hemifacial spasm, these demonstrated a significant improvement in functional outcome and spasm duration/day.[27] Several medications have historically been trialled in hemifacial spasm including carbamazepine and clonazepam. Small open-label studies suggest they can be effective although their efficacy can be inconsistent and wear off. Higher doses may also be required with potential sedative side effects. In general botulinum toxin is considered first line, although medications can be used if patients would prefer to avoid injections and a small trial has suggested that combined botulinum toxin and low-dose carbamazepine may provide better control than toxin alone. If the toxin fails, then surgical options, e.g. microvascular decompression are potential options and typically highly effective but come with a not insignificant risk of deafness and facial palsy.[28]

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* Sodium valproate should not be used in individuals of child-bearing potential given its potential teratogenic side effects.

Paroxysmal dyskinesias

The paroxysmal dyskinesias are a rare group of paroxysmal hyperkinetic movement disorders: predominantly chorea, ballism, and dystonia, which are considered to have a predominantly genetic aetiology. Only 20% are secondary to an acquired cause. They are subdivided into three groups depending on typical triggers: paroxysmal kinesigenic (PKD), paroxysmal non-kinesigenic (PNKD) and paroxysmal exercise induced dyskinesias (PED). Many genetic abnormalities are recognized. The type of paroxysmal dyskinesia can vary even in individuals with the same genetic abnormality.

In general treatment is symptomatic depending on the subtype of paroxysmal dyskinesia. For the acquired causes and certain genetic disorders, e.g. GLUT-1 deficiency associated with PED there may also be disease specific therapies. Due to the rarity of the disorders therapies are often based on clinical experience and case series in the absence of formal RCTs.[29]

Paroxysmal kinesigenic dyskinesia

PKD is characterized by brief (seconds to minutes) dystonic or choreiform movements of the limbs, trunk, or face. They are triggered by sudden movements and external stimuli. They are often associated with co-morbid epilepsy and migraines. They tend to respond well to ASMs particularly carbamazepine and other sodium channel blockers, e.g. lamotrigine and phenytoin. Levetiracetam, *valproate and topiramate may also be effective.

Paroxysmal non-kinesigenic dyskinesia

PNKD is characterized by prolonged (typically several hours) episodes of focal, or less commonly generalized, dystonia and/or chorea. They are typically triggered by fatigue, pregnancy, caffeine, alcohol, and tobacco. Management includes avoiding known triggers and benzodiazepines are often tried in an acute attack or as a prophylactic. Smaller case series have suggested that carbamazepine and other ASMs as used in PKD may be effective. If dystonia is prominent and persistent then agents used in typical dystonia can be used, e.g. trihexyphenidyl.

Paroxysmal exercise-induced dyskinesia

PED is characterized by the presence of dystonic movements following sustained exercise. This typically involves the feet but can affect the arms depending on the triggering activity. Attacks can last for minutes to hours. PED is associated with several different genetic disorders including

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* Sodium valproate should not be used in individuals of child-bearing potential given its potential teratogenic side effects.

GLUT-1 deficiency, DRD, and parkinsonian disorders. Other genetic mutations known to cause PKD and PNKD can also present in this fashion. Management strategies include trigger avoidance, and management based on the underlying abnormality: levodopa for DRD and parkinsonism, ketogenic diet for GLUT-1 deficiency. ASMs, clonazepam, and anti-cholinergic drugs used for dystonia may also work. If the symptoms are persistent targeted use of botulinum toxin or DBS may also be considered.

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Chapter 14

Dementia

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Introduction

Dementia is a progressive neurodegenerative disorder, which affects 5–10% of people aged over 65 worldwide. The commonest subtype is Alzheimer's disease (AD), estimated in the UK to account for ~60% of patients with dementia. This is followed by vascular dementia (VaD) (17%), Lewy body dementia (including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB)) (10–15%), frontotemporal dementia (FTD) (2%), and rarer forms. It is quite common for patients to suffer from two, or even three, pathologies, most commonly a combination of AD and VaD. Mixed dementia accounts for at least 10% of cases.

The DSM-5 defines dementia (specifically termed as a 'major neurocognitive disorder' in this edition) as an acquired significant cognitive impairment affecting a minimum of one of the following domains:

- learning and memory.
- social cognition.
- language.
- executive function.
- complex attention.
- perceptual motor function.

The deficit must cause significant impairment of activities of daily living and involve a continuous cognitive decline from a previous higher level of functioning. Dementia should only be diagnosed if the deficits cannot be attributed to delirium or psychiatric illness.

The management of dementia is multidisciplinary, with pharmacological treatment currently playing a relatively small role. Care should focus on ensuring appropriate coordination of health and social services. Drug treatments are used to allow patients to maintain their functional independence for as long as possible and then to aid the management of troublesome behaviours in late disease. Aducanumab is the only (at the time of writing) FDA-approved, potential disease-modifying therapy for Alzheimer's. It is not approved for use in the UK or EU.

Alzheimer's disease

AD is the commonest form of dementia, affecting as many as 30% of people aged over 90. AD usually occurs sporadically. It typically affects episodic memory first, and slowly progresses to involve other cognitive domains. Patients may ultimately experience a combination of problems, including language and visuospatial difficulties, dyspraxia, loss of executive functioning, and neuropsychiatric features.

Pharmacological treatment options depend on dementia severity. The most widely used method of measuring severity is the mini mental state examination (MMSE), which assesses orientation, recall, attention, calculation, language manipulation, and constructional praxis. The severity of AD is then stratified (maximum 30):

- mild: 21–26.
- moderate: 10–20.
- severe: <10.

Treatment

Symptomatic treatments

- Mild or moderate AD:
  - *First line*: donepezil, galantamine, or rivastigmine.
  - *Second line*: memantine (moderate AD).
- Severe AD:
  - memantine (donepezil and rivastigmine are licensed in the USA).
- Disease-modifying treatments
- Mild cognitive impairment and mild AD (USA only)
  - Aducanumab and lecanemab.

In the UK, NICE recommends that these drugs should be started by specialists and only continued if cognitive, functional, global, or behavioural symptoms improve on serial follow-up. NICE suggests that cost, side effects, drug adherence, co-morbidities, drug interactions, and dosing profiles should be considered when choosing the most appropriate of the three acetylcholinesterase inhibitors (AChEIs) (see Acetylcholinesterase inhibitors). Cost-effectiveness comparisons undertaken by NICE show little difference between the three AChEIs for mild to moderate AD. Memantine is less cost-effective in moderate AD than AChEIs and hence should be used second line for this indication. The AChEIs are relatively safe drugs; however, they can exacerbate bradycardia and cardiac arrhythmias, which should be borne in mind before offering treatment. The risks are thought to be equivalent among all available drugs.

Treatment withdrawal

Clinical improvement on AD medication within the first six months of initiation warrants long-term continuation for at least a year. One retrospective study suggested that the treatment effect may last up to five years for some patients. However, most patients will return to pre-treatment levels of cognition 12–18 months after initiation. It is important to stress that AChEIs can have pronounced beneficial effects on domains other than cognition that may justify continuation. There is, however, no consensus on how to quantify the clinical efficacy of treatment in severe AD (as the MMSE is a poor tool for discerning changes in cognitive ability at such severe levels of impairment) and thus when it may be appropriate to discontinue AChEIs or switch to memantine. In general, clinicians in the UK withdraw most AChEIs on a trial basis, to simplify drug regimes, as marketing authorization for AChEIs stops when an MMSE score of ten or less is reached. If there is a consequent sudden or drastic decline, treatment is restarted. In the USA, licensing for donepezil and rivastigmine is extended for severe disease, primarily due to the recognized benefits on behavioural symptoms.

Evidence base

AChEIs and memantine have been extensively investigated in AD. Multiple RCTs and meta-analyses have shown benefits of varying magnitude on cognition, behavioural symptoms (e.g. agitation, aggression), and functional outcomes (e.g. activities of daily living). Their safety and tolerability have also been assessed.

Cognition

A 2014 meta-analysis of RCTs assessing the efficacy of AChEIs and memantine in patients with mild to moderate AD, found statistically significant improvements in cognition, measured by differences in the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog) score, with treatment, when compared to placebo, for all medications. The score ranged from −1.29 points mean difference with 20 mg/day of memantine to −3.2 points mean difference with 32 mg/day of galantamine.[1] Head-to-head comparisons of AChEIs have not shown significant differences in efficacy between drugs of this class. A meta-analysis of two RCTs comparing AChEIs and memantine demonstrated that, in mild to moderate disease, memantine has a smaller impact on cognition than AChEIs.[2] Hence, it is used second line to the AChEIs for this indication.

Neuropsychiatric symptoms

There is conflicting evidence for a beneficial effect of AChEIs and memantine on behavioural components of AD (i.e. depression, anxiety, sleep disturbance, and aggression). Donepezil and galantamine both improved behavioural outcomes in some, but not all, trials. Two meta-analyses published in 2014 found a small improvement in behavioural symptoms with galantamine, but only one concluded that this was the case for donepezil. Memantine and the other AChEIs were not found to improve behaviour in either of these meta-analyses. As such, AChEIs and memantine are not licensed for treatment of these symptoms specifically, although the benefits can be used to justify continuing treatment in those already taking them, as is the case in the USA.

Monoclonal antibodies

Aducanumab and lecanemab have both recently received accelerated FDA approval for treatment of mild cognitive impairment and mild dementia in Alzheimer's disease. They are amyloid-beta directed monoclonal antibodies that act by binding aggregated amyloid-beta and promoting its subsequent removal via phagocytosis. They differ in their relative selectivity to soluble Aβ species vs. insoluble Aβ fibrils. This difference in selectivity may lead to differences in safety and efficacy, although there have been no head-to-head clinical trials. Aducanumab has a greater selectivity for insoluble fibrils, whilst lecanemab is more selective for soluble Aβ species.

Adecanumab is administered monthly, on an escalating dosing schedule to minimize the effect of amyloid-related imaging abnormalities (ARIA) such as oedema. Lecanemab is administered at a standard dose fortnightly and its licensing recommends repeated MRIs to look for evidence of ARIA over the first six months.

Adecanumab's licensing has incited some controversy. The FDA approved the medication under an accelerated approval pathway, based on the surrogate endpoint of reduction of amyloid-beta plaque load. Neither medication has yet been approved in the UK or Europe.

Evidence base

Two randomized, double-blind, phase III studies of aducanumab, EMERGE and ENGAGE, investigated adecanumab's efficacy in early AD.[3] Both studies were halted early based on futility analyses from the first 50% of enrolled patients. The studies demonstrated dose-dependent reduction in plasma p-tau and CSF p-tau and t-tau levels. CSFAβ1–42 increased in both studies. The primary efficacy endpoint, improvement in the clinical dementia rating scale (assessment of function and cognition in Alzheimer's) was met in EMERGE (difference of –0.39) for high dose aducanumab vs. placebo (p = 0.012 –22% decrease), but not ENGAGE (difference of 0.003 p = 0.833, 2% increase). ARIA-oedema occurred in 35–36% of the high-dose groups and 26% in the low-dose groups. ARIA-related microhaemorrhages and superficial siderosis were seen in 13–20% of the high-dose group patients. 20–29% of patients with ARIA reported symptoms, typically transient confusion, headache, and dizziness. Serious events occurred in 1.4–1.5% of the high-dose groups. These included delirium, generalized seizures, memory impairment, and gait disturbance.

A large RCT ($n = 1795$) of lecanemab vs. placebo[4] demonstrated an adjusted least-squares mean change in the clinical dementia rating—sum of boxes score, from baseline at 18 months of 1.21 with lecanemab vs. 1.66 with placebo (difference –0.45, p <0.001). ARIA was present in 12.6% of patients although not all were symptomatic.

Vascular dementia

VaD is the second most common cause of dementia. Diagnosis is made on the basis of the clinical features, the presence of vascular risk factors, and supportive neuro-imaging. There may be a stepwise accumulation of cognitive deficits, although onset can be subtle, probably due to accumulation of infarcts in non-eloquent areas of the brain or mixed pathology.

Treatment and evidence base

The treatment of VaD involves the prevention of recurrent strokes by modifying risk factors for cerebrovascular disease. The predominant modifiable risk factors include hypertension, diabetes mellitus, hypercholesterolaemia, alcohol intake, and smoking. Patients should be encouraged to cease smoking and reduce alcohol intake to acceptable levels, whilst their blood pressure, diabetic control, and cholesterol levels are optimized.

Risk factor management

Hypertension

Very high or consistently low blood pressure (BP) is associated with the development of VaD. There is some evidence that hypertension, particularly untreated hypertension in midlife, has a negative effect on cognition and can contribute to the development of dementia.[5,6] In older adults, the importance of maintaining a high enough BP to provide adequate cerebral perfusion has been highlighted, with studies suggesting that a persistently low BP increases the relative risk of dementia.

There are no published clinical trials assessing the effect of antihypertensive medication on reducing the risk of dementia or the rate of cognitive decline, as a primary endpoint, although several have included dementia as a secondary outcome measure.[7] The *SYST-EUR* (Systolic Hypertension in

Europe study), a randomized, placebo-controlled trial of nitrendipine, a calcium channel blocker (*n* = 2418) found that active treatment reduced dementia risk by 50% (3.8 vs. 7.7 per 1000 person-years; p = 0.05), with a median follow-up of 2 years. The *PROGRESS* study (Perindopril Protection against Recurrent Stroke study) (*n* = 6105) showed a non-significant reduction in risk of dementia by 12% in the treatment group. In a subgroup analysis of patients with recurrent stroke, there was a significant reduction in the risk of dementia by 34%. Hence, it is reasonable to control hypertension in patients who have had a stroke to prevent the occurrence of VaD.

Diabetes

Diabetes is an important risk factor for cardiovascular disease and stroke. One systematic review of 14 longitudinal studies found that co-existent diabetes increased the risk of developing VaD 2.5-fold.[8] Although no RCTs have investigated the effect of controlling blood glucose on the risk of developing, or the rate of progression of, VaD, observational studies have shown that rigorous control of blood glucose is inversely correlated with cognitive decline.

Hypercholesterolaemia

Epidemiological links between hypercholesterolaemia and VaD have been identified in several observational studies. Elevated cholesterol may also be linked to the risk of AD; however, this evidence is less clear. Although there is no clear evidence that statins and other lipid-lowering agents lower the risk of VaD in patients with high cholesterol, they do lower the risk of cardiovascular disease and stroke, and hence intuitively should reduce the risk of VaD.

Antiplatelet agents

Aspirin is widely used in the management of VaD; however, there are no RCTs to confirm that its use can reduce the risk of developing dementia or reduce the rate of cognitive decline in patients with existing VaD.[9]

Symptomatic treatment

Cholinesterase inhibitors and memantine

The justification for the use of cholinergic agents in VaD is based on the marked reduction in cholinergic markers found in the hippocampus, frontal areas, and temporal cortex in patients with this condition. Several meta-analyses show small cognitive improvements with AChEIs and memantine in patients with VaD.[10] However, the benefits are not significant enough to warrant licensing for VaD. Given the not infrequent association of VaD with AD and the difficulty in excluding AD in patients with VaD, off-label use is often practiced.

Dementia with Lewy bodies

DLB is characterized by progressive cognitive decline, combined with a triad of fluctuating cognition, recurrent visual hallucinations, and motor features of parkinsonism. It is often accompanied by REM sleep disorder and severe neuroleptic sensitivity. Dementia must precede or occur in the first year of onset of parkinsonism in order to distinguish DLB from PDD. Management includes early detection, investigation, and treatment of cognitive impairment. Behavioural and neuropsychiatric symptoms, movement disorders, autonomic dysfunction, and sleep disorders should also be addressed. Cognitive dysfunction and neuropsychiatric symptoms can be improved by educating patients and caregivers on the nature of the disease and increasing social interaction and environmental stimuli.

The pharmacological management of DLB is challenging because of the mixture of autonomic, neuropsychiatric, cognitive, and motor dysfunction. These features tend to be unpredictable, and treatment of one may exacerbate the other. This particularly applies to the treatment of neuropsychiatric symptoms and parkinsonism, which may exacerbate each other. General management principles of dysautonomia and sleep in DLB and PDD are discussed further in Chapter 12, Parkinson's disease and parkinsonism, Chapter 20, Uro-neurology, and Chapter 17, Sleep disorders, respectively.

Treatment

Cognitive and neuropsychiatric symptoms

- *First line*: Acetylcholinesterase inhibitors
- *Second line*: Antipsychotics

Rivastigmine is licensed for use in PDD in the UK and USA for its behavioural, rather than cognitive, benefits. As many consider DLB and PDD as a disease spectrum, it is also frequently used in DLB. Donepezil has also been demonstrated to improve cognition and caregiver burden, and is frequently used off-label in the treatment of DLB. Similarly galantamine has been demonstrated to reduce hallucinations and other neuropsychiatric parameters in DLB, although use in this setting is again off-label. Memantine may also improve attention and executive function in patients with DLB.[11] Its use is off-label. It can be used as monotherapy if AChEIs are not tolerated or contraindicated, or in combination if the response to AChEIs is insufficient.[12,13]

These agents are used to aid different components of cognition, particularly memory, attention, and executive functioning, but are also frequently used first line for neuropsychiatric symptoms such as hallucinations, delusions, and apathy.

Antipsychotics can be used but they pose a significant risk of aggravating confusion and motor symptoms. Patients with DLB and PDD can be highly sensitive to these antipsychotics and their use is associated with increased mortality in Dementia and Parkinson's disease. They should only be used after careful consideration of their potential benefits and risks.

Motor symptoms

In general, motor symptoms are not the dominant problem in DLB. A number of medications used to treat the motor symptoms of parkinsonism will have additional cognitive and neuropsychiatric risks in this patient group. If required, levodopa is typically used at low dose as a monotherapy. Exacerbating co-morbidities such as constipation and concurrent infections should be considered and treated. AChEIs may exacerbate the motor symptoms of Parkinson's although in clinical practice this is rare and typically mild.

Evidence base

Rivastigmine

In one 20-week, double-blind, placebo-controlled trial of 120 patients with DLB given either 6–12 mg/day rivastigmine or placebo,[14] 63% of the rivastigmine arm showed at least a 30% improvement in baseline neuropsychiatric testing, compared to placebo ($p = 0.001$). Symptom domains improving with rivastigmine included apathy, anxiety, indifference, delusions, hallucinations, aberrant motor activity, and attention. There was no effect on the MMSE or clinical global change-plus scale.

Donepezil

In a 12-week RCT of 140 patients,[15] mean changes in MMSE scores were significantly higher in the donepezil-treated groups (5 mg: 3.4, $p < 0.0001$; 10 mg: 2.0, $p < 0.001$) than the placebo group (−0.4). Statistically significant improvements in behaviour were also noted compared with placebo (5 mg: −5.80, 95% CI −12.4 to 0.8, $p = 0.047$; 10 mg: −8.3, 95% CI −15.8 to −0.9, $p = 0.019$). Caregiver burden was significantly reduced with 10 mg/day of donepezil, compared with placebo (mean change in Zarit caregiver burden inventory of −9.2, 95% CI −15.3 to −3.0), but not with 5 mg/day.

Memantine

In a meta-analysis[16] memantine was shown to improve attention and executive function, although there were no clear changes in global cognitive function as assessed by MMSE or Montreal Cognitive Assessment (MoCA) assessments.

Parkinson's disease dementia

Dementia is estimated to occur in 31–41% of patients with PD. PDD is diagnosed when a patient who has had PD for 1 year or more develops dementia. Compared to AD, the cognitive decline is characterized predominantly by attention, visuo-perceptive, and visuo-constructive deficits.

The management is very similar to that of DLB with the exception that patients with PDD may already be taking several therapies for symptomatic control of the motor features of Parkinson's disease. These medications may now be exacerbating the cognitive and neuropsychiatric features seen with more diffuse Lewy body pathology. Usually, significant improvement of these symptoms and overall functioning of a patient can be achieved by reducing and simplifying the medication regimen. Anticholinergics, dopamine agonists, and amantadine, among others are withdrawn where possible.

Treatment of cognitive and neuropsychiatric symptoms

- *First line*: AChEIs (see DLB)
- Similar medications are used in PDD as in DLB although there are less supportive trials for this patient group.

Evidence base

Of the anti-dementia drugs, rivastigmine has the strongest body of evidence. The *EXPRESS* study (EXelon in PaRkinson's disEaSe dementia study) was a parallel-group, double-blind, placebo-controlled trial ($n = 541$) investigating the use of rivastigmine in patients with PD and mild to moderate dementia (MMSE 10–24).[17] Those in the treatment arm showed an 8.8% improvement from baseline cognitive scale scores, while the placebo arm showed a 2.9% worsening ($p < 0.001$). Deterioration of parkinsonian symptoms (particularly tremors) was reported more frequently in the treatment arm (27%, compared to 16%); however, this was not statistically significant.

Trials investigating the effects of donepezil, galantamine, and memantine have not shown convincing evidence of cognitive improvement. Of the drugs used to treat PDD, the MDS evidence-based review found only rivastigmine to be clinically useful in PDD.

Frontotemporal dementia

The FTDs are a group of clinical syndromes in which degeneration of the frontal and anterior temporal lobes occurs. Although the syndromes are clinically and pathologically heterogeneous, abnormal behaviour predominates in FTD.

Treatment

There is some evidence to suggest that multimodal rehabilitation for patients and education for caregivers are useful. There is very little evidence that pharmacological interventions help. SSRIs and antipsychotics may be used for the management of behavioural problems, based on evidence from small trials and case series. CNS stimulants, e.g. dexamfetamine and methylphenidate, have also been used to manage behavioural problems. However, different trials have given conflicting results, hence their use is still considered experimental. There is no convincing evidence that AChEIs or memantine modify behaviour or improve cognition in FTD.

Mixed dementia

Pathological studies have suggested that coexisting vascular pathology exists in around 25% of patients with AD. Additionally, pathological PD is present in around 25% of AD patients, and 50% of cases of DLB are associated with AD pathology.

Treatment

There have been a relatively small number of trials of AChEIs in mixed dementia. However, given that mixed dementia is an overlap of pathologies, treatment benefits may be extrapolated from trials in other forms of dementia. Mixed dementia should be managed according to the condition that is thought to be predominant.

Evidence base

There is very little trial data to inform the management of mixed dementia. Evidence for use of different agents is derived from trials in presumed, purer forms of dementia. There are small placebo-controlled studies of patients with AD and vascular risk factors, and Alzheimer's with cerebrovascular disease, suggesting that rivastigmine and galantamine respectively, result in significant improvement in both cognitive scores and scales of activities of daily living. Hence it is reasonable to consider a trial of AChEIs if there is suspicion that the patient's dementia syndrome is in part due to Alzheimer's or Lewy body pathology.

Mild cognitive impairment

The National Institute on Aging–Alzheimer's Association has suggested the following features as core clinical criteria for mild cognitive impairment (MCI):

1. A fall in cognition reported by a patient or informant, or observed by a clinician;
2. An objective impairment in one or more cognitive domains, usually including memory;
3. No change in functional independence;
4. No dementia.

The DSM-V uses the term mild neurocognitive disorder, to describe a similar syndrome with moderate cognitive decline that does not interfere with independence.

MCI may be a precursor to several neurodegenerative pathologies. The specific cognitive deficit may differ depending on the underlying pathology. The amnestic subtype is the most common, 5–10% of patients in this cohort progressing to AD annually. MCI remains, however, a somewhat contentious diagnosis, and some studies have reported that around 40% of those diagnosed will revert to normal over 1–3 years. There are no licensed treatments for MCI. Trials have produced conflicting data. A 2012 Cochrane review of nine double-blind, placebo-controlled trials assessing the use of AChEIs in patients with MCI ($n = 5149$) established that AChEIs did not significantly improve cognitive test scores or convincingly prevent progression to dementia.[18]

The focus of pharmacological care is treating co-morbidities such as mood disorders and obstructive sleep apnoea which can cause or exacerbate cognitive complaints and withdrawal of medications associated with anticholinergic or sedative side effects. Treatment of vascular risk factors, if present, should also be optimized.

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Chapter 15

Spasticity

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Introduction

Spasticity is a velocity-dependent increase in muscle tone seen in an upper motor neuron (UMN) syndrome. It is most commonly seen in multiple sclerosis (MS), stroke, and cerebral palsy, but it may also occur with any pathology that involves central motor pathways. In general, spasticity develops gradually over days, weeks, and months, following the development of a UMN lesion.

On examination, tone of the affected limb(s) is increased and resistance is increased on passive stretch in a velocity-dependent manner, as exemplified by the supinator catch. Spasticity is usually accompanied by other UMN signs, including pyramidal pattern weakness, brisk reflexes, clonus, posturing, and extensor plantar responses. Sometimes, a 'clasp-knife' phenomenon is seen where more sustained force leads to a sudden, paradoxical reduction in tone. Spasticity can generally be distinguished clinically from other causes of increased tone, including rigidity, gegenhalten, and catatonia. The severity of spasticity may vary considerably, from being a clinical sign with no functional impact to a painful increase in tone interfering with mobility, transfers, and personal care. Severe untreated spasticity may result in secondary biomechanical effects, including tendon shortening, contractures, and heterotopic ossification.

Treatment

Not all patients with spasticity require pharmacological treatment. In some, spasticity may provide functional benefit, e.g. spasticity in hip and knee extensors can aid standing and transfers, and in such patients, muscle weakness resulting from high dose oral anti-spasticity agents could be detrimental. In general, patients with problematic spasticity are best managed by a multidisciplinary rehabilitation team using a goal-centred approach.

Non-pharmacological methods of treatment

- *Physiotherapy and occupational therapy*: splinting and positioning programmes (such as with a T roll or an upper limb splint), and regular standing in a standing frame can be helpful. Stretching and exercise, however, do not appear to have a significant effect on spasticity per se, although exercise may improve strength and function. A specialist wheelchair and seating assessment may also help with tone management.
- *Treatment of exacerbating factors*: nociceptive, visceral, or somatic stimuli, including pressure sores, chronic urinary retention, or constipation, may all have an impact upon spasticity and should be treated.

Surgery: operative interventions can be useful in specific circumstances. A selective dorsal rhizotomy may be an option for young people with cerebral palsy. Other surgical options include tendon lengthening procedures to improve range and movement

Pharmacological treatments

If medical treatment is required, a goal-orientated approach is generally adopted. For instance, in a patient with a spastic paraparesis, the aim might be to relieve nocturnal spasms which disrupt sleep or to alleviate leg stiffness and clonus when standing and walking. Following a stroke, spasticity at the elbow, or elsewhere in the affected arm, which has not responded adequately to early physiotherapy and splinting, may benefit from botulinum toxin injections.

When oral anti-spasticity agents are used, a ‘start low and go slow’ approach can avoid the unwanted side effects of sedation and weakness often seen with inappropriate dose escalation.[1,2] Medical spasticity management can be divided into systemic and localized treatments.

Systemic agents

- *First line*: baclofen, gabapentin, tizanidine.
- *Second line*: dantrolene.
- *Adjuncts*: pregabalin, cannabinoids, or benzodiazepines.

The $GABA_B$ receptor agonist baclofen or the $\alpha 2$-adrenergic antagonist tizanidine are usually first-line options. The efficacy of both drugs is comparable, but their side effect profiles differ. Occasionally patients will end up taking both. Dantrolene acts directly on muscle tissue, and it can have a useful role as a second-line agent when baclofen and tizanidine are not tolerated.[2,3] It does carry a risk of hepatitis, and careful monitoring of liver function tests is required.

Benzodiazepines such as clonazepam may be particularly useful for intermittent spasms, especially when sleep is disrupted.

Gabapentin and pregabalin can be used as an adjunct to first-line th4erapies and they are also useful for myelopathic pain.[4]

A cannabinoid oromucosal spray is licensed for the second-line treatment of spasticity in MS in UK.

Evidence base

A 2003 Cochrane database meta-analysis of anti-spasticity agents in MS included 26 placebo-controlled studies and 13 comparative studies. Only 15 of these studies used the Ashworth scale (a reliable measure of spasticity used to gauge the effectiveness of an anti-spasticity agent), and only three of the eight placebo-controlled trials showed a statistically significant difference. Many studies were of low quality. The authors concluded that no recommendations could be made for prescribing.[5] There are even fewer data for the use of oral anti-spasticity agents in other conditions (with only a very limited number of small controlled studies in stroke, cerebral palsy, and spinal cord injury, and no definitive comparative data).[6] A number of randomized placebo-controlled trials have shown that cannabinoids reduce spasticity.[7–9]

Localized treatments

1. *Botulinum toxin*: botulinum toxin injections are commonly used to treat focal or multifocal spasticity. For example, botulinum toxin may be useful in a stroke patient with a spastic upper limb (where the elbow, wrist, and fingers are held in a flexed position) when there is inadequate response to splinting. Injections are given to a specific muscle or to several muscles. The effect wears off over 3–4 months, as nerve terminals re-sprout.

Evidence base

The UK Royal College of Physicians published guidelines listing 13 studies (ten placebo-controlled trials) using botulinum toxin to treat upper limb spasticity in stroke, traumatic brain injury, or in a mixture of CNS disorders, with evidence for a reduction in tone and some evidence for an improvement in function. Eight studies (six controlled trials, with one parallel study) investigated lower limb spasticity. There was some evidence for reduction in tone and functional improvement.[10]

2. *Phenol and alcohol ablation*: these neurolytic agents are sometimes used to treat focal spasticity, usually when lower limb regional spasticity involves large muscles when the dose limits for botulinum toxin injections would be exceeded. Nerves targeted with phenol might include the obturator nerve for adductor spasm and the sciatic nerve for hamstring spasms. Spasticity may recur after several months.

A randomized-controlled pilot study comparing phenol and alcohol neurolysis of the tibial nerve after stroke found that both were effective at reducing spasticity but that alcohol neurolysis seemed to have more sustained benefits.[11,12]

3. *Intrathecal baclofen*: if lower limb spasticity remains severe, despite a trial of oral agents at adequate doses and a period of rehabilitation, an intrathecal baclofen pump or intrathecal phenol administration may be indicated. Such a patient may have severe hamstring spasticity preventing them from sitting out and/or severe hip adductor spasm, leading to difficulty in maintaining perineal hygiene and skin integrity. A baclofen pump is implanted surgically within the subcutaneous tissue overlying the abdomen. A catheter tracks subcutaneously from the pump to the lumbar subarachnoid space, and baclofen is infused continuously into this compartment. This allows concentrated doses to be infused into the lumbar intrathecal space while reducing systemic side effects. The pump is programmed by a computer-controlled handheld device, and refilled with a needle every few months. Complications include pump infection, and there is a danger of severe rebound spasticity, if the pump is allowed to run out.

Many case series of intrathecal baclofen treatment have shown improvements in Ashworth scores in patients previously unresponsive to oral therapy.[13]

4. *Intrathecal phenol:* this involves administration of phenol into the lumbar subarachnoid space. Typically, 1–2 injections are required, which should result in a long-term reduction in spasticity. Intrathecal phenol is reserved for patients with no functional lower limb movement and who have already lost bladder, bowel, and sexual function, and when other options have failed.

A case series of patients with quadriplegia showed that lower limb spasticity was reduced in most patients, following an intrathecal phenol injection, but that some spasticity eventually returned in 80%.[14]

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Chapter 16

Neuro-oncology

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Introduction

Primary central nervous system (CNS) tumours

Globally, primary CNS tumours account for approximately 2% of adult, and 20% of childhood cancers. In addition, due to progressive neurological deficits and overall poor prognosis for many subtypes, they are responsible for a disproportionate share of cancer morbidity and mortality. As they often affect younger people, they are responsible for more years of life lost than any other cancer and they place an enormous burden of suffering on patients, their families, and carers.

CNS metastases

In adults, brain metastases are 3 times more common than malignant primary CNS tumours. The commonest primary sources are lung cancer (30–60% of all cases, and the commonest source in men), breast cancer (20–30% of all cases, and the commonest source in women), melanoma, renal, and colorectal cancer. Overall 10–30% of patients with newly diagnosed cancer develop brain metastases. Metastases also occur in the leptomeningeal (4–15% of cancer patients), spinal epidural (5–10% of cancer patients), and dural (8–9% of cancer patients) spaces.

Classification

Primary CNS tumours

There are over 180 different types of primary CNS tumours, according to the most recent WHO classification of brain tumours (2021).[1] The WHO classification is based both on histology and molecular features. Tumour grade is assigned according to specific histological criteria (see Table 13.1), as well as by molecular features (e.g. CDKN2A/B homozygous deletion). Grades 1 and 2 are considered low-grade, whilst grades 3 and 4 are considered high-grade, malignant neoplasms.[2,3]

Meningiomas are the most frequent type of CNS tumour, accounting for ~38% of cases.[4] They arise from the meninges and typically grow slowly (most are benign, i.e. Grade 1). On MRI, they are extra-axial and enhance homogenously with contrast. They cause focal neurological deficits) through mass effect as well as seizures. Most cases are curable by gross total resection or controllable with radiotherapy.

Gliomas are the second most common type of primary CNS tumour. They account for ~25% of cases. These are thought to arise from glial cells and, with the exception of grade 1 tumours, infiltrate the brain. They vary from low-grade benign tumours (e.g. pilocytic astrocytomas), to high-grade malignant tumours (e.g. glioblastomas). Most frequent subtypes are astrocytomas, oligodendrogliomas, and ependymomas. Lesions are T2-FLAIR hyperintense and often demonstrate contrast enhancement.

Oligodendroglioma: An infiltrating glioma characterized by an isocitrate dehydrogenase (IDH) mutation as well as codeletion of the short arm of chromosome 1 and the long arm of chromosome 9 (1p/19q codeletion). They typically present with seizures in 30–50-year-olds. They can be grade 2 or 3 (anaplastic).

Table 13.1 WHO grading system for CNS tumours

Grade	Features	Prognosis (median life expectancy)
1	Low proliferative potential.	Excellent (cure is possible after complete surgical resection)
2	Low proliferative potential but infiltrating, with high rate of recurrence and progression to higher grades.	Variable. Depends on histological subtype and resectability. 5–15 years
3	Infiltrating tumours with marked evidence of nuclear atypia and often evidence of brisk mitotic activity. Either microvascular proliferation or necrosis might be present.	2–3 years
4	Highly mitotically active, infiltrating neoplasms with marked nuclear atypia and the presence of both microvascular proliferation and necrosis.	1–2 years

Adapted from Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., WHO Classification of Tumours of the Central Nervous System, Fifth Edition (2016), with permission from International Agency for Research on Cancer.

IDH-mutant astrocytomas: Infiltrating gliomas affecting 35–50-year-olds. They are characterized by mutations in IDH. Based on histology and presence of homozygous deletion of CDKN2A/B, they can be grade 2 (no anaplastic features or CDKN2A/B deletion), grade 3 (anaplastic features but no CDKN2/A deletion) or grade 4 (CDKN2A/B deletion regardless of histology).

IDH-wild type astrocytomas: Infiltrating gliomas without mutations in IDH. They can be grade 2 (no anaplastic features; rare), grade 3 (anaplastic features) or grade 4, designated as glioblastoma (GBM) with anaplastic features and microvascular proliferation and necrosis on histology OR diffuse astrocytic histology and at least one of the following: EGFR amplification, combined whole chromosome 7 gain and whole chromosome 10 loss or TERT promoter mutation). GBM prognosis is very poor, with median survival of 3–6 months untreated and 16 months if treated optimally with surgery and chemoradiation. For all astrocytomas, methylation of the MGMT gene promoter is associated with better prognosis as it correlates with improved response to alkylating chemotherapy such as temozolomide (TMZ).

Primary CNS lymphoma (PCNSL) is an extra-nodal diffuse large B-cell lymphoma confined to the CNS. It accounts for 3% of primary brain tumours. Most cases occur in immunocompetent individuals but PCNSL is occasionally seen in immunodeficiency states. Lesions often demonstrate homogenous enhancement (peripheral enhancement in immunosuppressed) and shrink rapidly with corticosteroids, hence these should be avoided if possible where there is clinical suspicion before definitive surgical biopsy (no role for resection in most patients). PCNSL is rapidly progressive but median survival in younger patients is considerably better than malignant gliomas. Fitness to endure aggressive chemotherapy is determined on the basis of organ function (renal and cardiac) and comorbidities rather than chronological age (performance status often improves following initial therapy). High-dose methotrexate is the mainstay of treatment for first-line remission induction This is often combined with rituximab and oral TMZ. Whole brain radiotherapy is a first-line option for patients unable to tolerate chemotherapy. Multiple consolidation strategies are being evaluated, including high-dose chemotherapy followed by autologous stem cell bone marrow transplant. The 5-year survival rates can be as high as 80% in this group, but, for the majority of patients, median survival is about 60% at 2 years.

Treatment

The main treatment modalities used in the management of CNS tumours comprise surgery, chemotherapy, and radiotherapy (RT). Treatment selection depends on a number of factors, including patient age and performance status, tumour location, histology, and molecular features (see Table 13.2).[5–7]

Table 13.2 General treatment approaches for common CNS tumours

Tumour	First-line treatment	Treatment of recurrence*
Meningioma	Observation with serial imaging if asymptomatic, particularly if =< 3 cm. If the patient is a surgical candidate, complete resection can be curative if grade 1. RT is required for grade 3 tumours and should be considered for incompletely resected grade 2 tumours.	Further surgery or radiotherapy.
Oligodendroglioma	Maximal safe resection. In grade 2, if patient </= 40 yo and complete resection, observe with serial imaging or consider clinical trial. If incomplete resection or >40 yo, post-operative RT + temozolomide or procarbazine, lomustine, and vincristine (PCV), or clinical trial (preferred). If grade 3, post-operative RT + PCV or temozolomide, or consider clinical trial (preferred).	Consider clinical trial (preferred), resection, repeat RT or TMZ, lomustine, or carmustine or PCV, bevacizumab or carmustine or lomustine + _ bevacizumab or TMZ + bevacizumab.

Table 13.2 (*Contd.*)

Tumour	First-line treatment	Treatment of recurrence*
IDH-mutant astrocytoma	Maximal safe resection. In grade 2, if patient </= 40yo and complete resection, observe with serial imaging or consider clinical trial (preferred). If incomplete resection or > 40yo, post-operative RT + temozolomide or PCV, or clinical trial (preferred). If grade 3 or 4, post-operative RT + temozolomide, or consider clinical trial (preferred).	Consider clinical trial (preferred), re-resection, additional cycles of adjuvant chemotherapy, repeat RT or TMZ, lomustine or carmustine or PCV, bevacizumab or carmustine or TMZ, lomustine + _ bevacizumab or TMZ + bevacizumab.
Glioblastoma, IDH-wild-type, WHO grade 4	Maximal safe resection. If histological grade 2, genotyping to evaluate for high-grade features, if available Monitor closely with MRI every 3 months or if subtotal resection, treat with concurrent RT and temozolomide + adjuvant temozolomide. If grade 3 or 4, post-operative RT with temozolomide + adjuvant temozolomide + tumour-treatingfields device, or clinical trial (preferred).	Consider clinical trial (preferred), re-resection, repeat RT, or systemic therapy or palliative therapy.
Primary CNS lymphoma	Induction with a high-dose methotrexate-based regimen or whole brain RT (WBRT) if not a candidate for systemic chemotherapy. For consolidation, consider systemic therapy with or without high-dose stem cell bone marrow rescue or clinical trial[8] or low-dose WBRT with or without temozolomide.	Consider clinical trial or systemic and/or intra-CSF therapy, or re-treat with high-dose methotrexate systemic therapy ± other therapy (if able to tolerate) or WBRT or involved-field RT (if eligible) or palliative care.
Brain metastases	Resection for a single, large, surgically accessible, symptomatic metastasis in patients with controlled systemic disease, followed by stereotactic radiosurgery (SRS) to the resection cavity or WBRT +/– memantine or palliative care for disseminated disease with poor systemic treatment options. WBRT for > 10 metastases.[9]	All treatment modalities can be considered taking into account first-line treatment, degree of systemic disease control and patient performance status.

* Repeat resection of recurrent brain tumours is only considered in a minority and depends upon accessibility and eloquence of the tumour site and patient performance status.

1. *Surgery*: surgery is important for establishing a tissue diagnosis, resection (potentially curative in grade 1 tumours, particularly grade 1 gliomas and meningiomas, survival benefit in higher-grade tumours), and relief of mass effect complications, e.g. tumour debulking and shunting for obstructive hydrocephalus. Resection is rarely curative in the context of intra-axial adult low-grade gliomas, because of the degree of localized spread prior to resection, but gross total resection of all the hyperintense T2-FLAIR areas extends survival.
2. *Radiotherapy*: radiotherapy can be administered as external beam radiotherapy, directed at the tumour mass, or whole brain radiotherapy, the latter usually reserved for extensive brain metastases or PCNSL. Primary brain tumours are treated with conformal fractionated radiotherapy, delivered over several weeks, or with highly focused treatment as either fractionated stereotactic radiotherapy or single-fraction stereotactic radiosurgery. Stereotactic radiosurgical techniques (SRT) are commonly used to treat small (up to a maximum diameter of 3–4 cm and up to a maximum volume of 20 cc in multiple lesions), localized extra-axial brain tumours, which are situated close to important structures, and cerebral metastases.
3. *Chemotherapy*: brain tumour sensitivity to chemotherapy depends on tumour type. In addition, the blood-brain barrier limits access of systemically administered hydrophilic chemotherapeutic agents to the CNS. High-grade gliomas are most commonly treated with the oral alkylating agent temozolomide, or in the case of anaplastic oligodendroglioma with the combination of procarbazine, lomustine, and vincristine (PCV regimen).[10] Bevacizumab, an anti-VEGF monoclonal antibody, impairs tumour angiogenesis and improves vasogenic oedema. It does not prolong survival in high-grade glioma but is used for palliation. Chemotherapy is associated with significant side effects, most commonly myelosuppression. Patient age, performance status, tumour grade and type, side effect profile of the different agents, and patient preference should inform treatment decisions.

Management of complications

Raised intracranial pressure

Clinical features of raised intracranial pressure (ICP) include headache, vomiting, and visual disturbance (obscurations, scotomata, or enlarged blind spots, diplopia), progressing to Cushing's triad of bradycardia, hypertension, and respiratory depression, and ultimately to depressed consciousness and coma. There may be focal neurological deficits from the underlying pathology, and false localizing signs, such as VI nerve palsies, and herniation syndromes.

Raised ICP is the final common pathway for many intra- and extracerebral pathologies, the commonest mechanisms being CSF accumulation, mass effect, venous congestion, or vasogenic oedema, either alone or in combination. Raised ICP in brain tumour patients due to vasogenic oedema and mass effect is usually treated with corticosteroids and surgical debulking, the urgency of which is dictated by the patient's neurological deficits. The vast majority of patients with brain tumours have normal levels of consciousness and therefore can be treated with oral dexamethasone. Administration via the intravenous route is typically reserved for patients with depressed consciousness or peri-operatively. Dexamethasone is the preferred corticosteroid due to its significantly lower mineralocorticoid effect, and long half-life. Maintenance therapy is usually given orally at 2–16 mg/day in 1–4 divided doses, depending on the degree of oedema and initial response. Corticosteroids should be weaned as soon as possible to prevent complications of hypercortisolism (obesity, hyperglycaemia, hypertension, osteopenia) and opportunistic infections.[11]

Emergency management of acute intracranial hypertension in the context of CNS malignancy is similar to that occurring as a consequence of severe vascular and infective processes. It is best carried out with intensive care and neurosurgical input. Detailed management is beyond the scope of this book but the broad principles include:

1. Treating factors that can further raise ICP, including seizures, hypoxia, hypercapnoea, and hypertension secondary to pain or agitation.
2. ICP reduction with hyperosmolar therapy, either intravenous hypertonic saline or mannitol.[12]
3. Dexamethasone 8–16 mg to control vasogenic oedema.
4. Definitive surgical management with surgical evacuation/debulking of brain lesions, CSF drainage/shunting, or decompressive craniectomy where indicated.

Seizures

Seizures are common complications of CNS tumours and their treatment (surgery, RT). An estimated 60–80% of patients with gliomas experience seizures during the course of their illness. Seizures are frequently the presenting symptom of low-grade gliomas and are typically of focal origin, with or without secondary generalization. Brain tumour related seizures warrant indefinite anti-seizure medications. Levetiracetam is now widely used as first-line treatment, given its effectiveness, favourable side-effect profile, and lack of drug interactions. Alternative treatments are discussed in Chapter 3, Epilepsy, but, in general, drugs that act as inducers of cytochrome p450 enzymes (phenytoin, carbamazepine, oxcarbazepine, and phenobarbital) should be avoided. Despite the high prevalence of seizures in brain tumour patients, the American Academy of Neurology advises against treatment with prophylactic anti-seizure medications in patients who have not yet had a seizure.[13,14]

Vascular complications

Haemorrhage into a high-grade primary brain tumour or metastasis is common, and can cause acute headache, changes in mental status and focal neurological deficits. Thrombocytopenia due to chemotherapy, as well as treatment with anti-VEGF agents, increases the risk of intracerebral haemorrhage. After prompt diagnosis with CT head, management requires discontinuation of antiplatelet and anticoagulant agents, treatment of brain oedema (see earlier) and consideration of surgical evacuation. Cerebral infarctions also occur more commonly in brain tumour patients, risk increased by radiation vasculopathy and arterial or venous thrombosis in the setting of hypercoagulability of malignancy or anti-VEGF therapy.

Intravenous recombinant tissue plasminogen activator is contraindicated in patients with intra-axial tumours given the high risk of intracranial haemorrhage but mechanical thrombectomy can be considered if clinically indicated. For venous sinus thrombosis in the setting of hypercoagulability of malignancy, therapeutic anticoagulation is indicated. Antiplatelet monotherapy is often used for radiation vasculopathy although it is unclear if it changes the course of the disease.

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Chapter 17

Sleep disorders

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Introduction

Sleep disorders are very common and are frequently underdiagnosed. They have a significant impact on public health and productivity, with substantial financial implications for society. Mechanisms regulating normal sleep and sleep disorders are incompletely understood. This has implications for effective management, as causative mechanisms are only rarely the direct target for treatment. Many compounds discussed in this chapter are used off-licence, based on case studies and clinical experience.

Classification

The International Classification of Sleep Disorders, third edition (ICSD-3) divides sleep disorders into seven major categories[1]:

1. Insomnia.
2. Sleep-related breathing disorders including sleep apnoea syndromes.
3. Central disorders of hypersomnolence including narcolepsy.
4. Circadian rhythm sleep–wake disorders.
5. Parasomnias including disorders of arousal in non-REM (rapid eye movement) sleep and RBD (REM sleep behaviour disorder).
6. Sleep-related movement disorders including restless legs syndrome and the closely related periodic limb movements of sleep (PLMS).
7. Other sleep disorders.

Management of sleep disorders

With all sleep disorders, it is important to identify and treat co-morbid conditions such as obstructive sleep apnoea (OSA), nocturia, pain, and mood disorders, all of which may aggravate an underlying sleep disorder and further impair the quality of sleep.

OSA is not discussed further but the diagnosis should be considered in all patients with poor quality sleep, especially if they exhibit central obesity and report symptoms such as excessive daytime sleepiness, headache on waking, CO_2 retention, and/or nocturnal apnoeic episodes.

Insomnia

Insomnia is the commonest sleep complaint, affecting up to 10–15% of the general population. It is defined variably as a chronic difficulty in achieving or maintaining adequate sleep despite sufficient opportunity to do so, such that sleep is non-restorative and results in daytime functional impairment or distress.

Patients should be informed to avoid substances and prescribed medications such as alcohol, nicotine, caffeine, and other stimulants, which can impair sleep. They should also be given sleep hygiene advice.

Treatment and evidence basis

A wide range of drugs are used in the treatment of insomnia, with a variable level of evidence to support their efficacy. The European Insomnia

Guidelines[2] and British Association of Psychopharmacology consensus statement on evidence-based treatment of insomnia[3] are summarized next:

Non-pharmacological approaches

There are several longer-term treatment options. Psychological approaches such as cognitive behaviour therapy that focuses specifically on insomnia (CBT-I) are often effective and are not associated with significant long-term side effects.

Pharmacological approaches

Melatonin

Prolonged-release melatonin is licensed for use in insomnia in people over 55 years of age. This is usually well tolerated. It has been investigated in several RCTs and resulted in a clinically significant improvement in sleep compared to placebo.[7] A further RCT suggested that this effect was maintained for up to 3 months but not by 6 months.

Benzodiazepines and Z-drugs

Several controlled trials support short-term use of both benzodiazepines and the benzodiazepine receptor agonists: 'Z-drugs' (eszopiclone, zopiclone, zolpidem, and zaleplon). Both drug classes enhance the inhibitory effect of γ-aminobutyric acid (GABA). Although the Z-drugs were initially marketed as more effective and less addictive than the benzodiazepines, meta-analyses and reviews suggest there is little added benefit of Z-drugs over short-acting benzodiazepines, such as temazepam, although well-controlled comparative studies are lacking. Agents with shorter half-lives reduce the chance of a morning 'hangover' effect.

All benzodiazepines and Z-drugs have the potential for tolerance and addiction, and hence their use for primary insomnia should generally be restricted to as short a duration as possible, typically 3–5 days, certainly less than 2 weeks. They are typically reserved for scenarios where sleep hygiene measures have been unsuccessful, and insomnia is causing significant distress.

Orexin receptor antagonists

The FDA has recently approved a new class of agents, orexin receptor antagonists. These include daridorexant, lemborexant, and suvorexant. These medications are licensed for the treatment of sleep-onset and sleep-maintenance insomnia. Suvorexant and daridorexant are non-selective orexin 1 and 2 inhibitors, whilst lemborexant is a selective orexin 2 inhibitor. There are no head-to-head studies, but randomized placebo-controlled studies have shown them all to be effective.[4–6] Their main side effect is morning hypersomnolence. A significant advantage is s that they appear to have low abuse potential.

Off-label pharmacological approaches

In clinical practice, several pharmacological agents are commonly used for the treatment of chronic insomnia. Most major guidelines do not recommend routine use of hypnotic agents due to low-quality trial evidence, significant side-effect profiles, and limited long-term data on benefit.

Antidepressants:

Tricyclic antidepressants and trazadone are commonly used because of their sedative properties, thought partly to reflect an anti-histaminergic property. However, no studies have demonstrated that tricyclic antidepressants or alternative agents such as trazadone improve sleep in the long term. Cardiovascular and anticholinergic side effects can also be seen, particularly in the elderly population.

Anti-seizure medications (ASMs)

Although not licensed for insomnia, ASMs are occasionally used for sleep-related problems. Valproate, gabapentin, and pregabalin are the most used agents. The latter two are helpful if there is co-morbid restless legs syndrome or pain. There is limited evidence of long-term efficacy in the management of isolated insomnia and their side-effect profile argues against their use in the absence of these co-morbidities.

Narcolepsy

Narcolepsy is a central hypersomnia characterized by impaired regulation of the sleep–wake cycle, resulting in poorly maintained wakefulness and sleep. Elements of REM sleep such as paralysis and hallucinatory experiences intrude into wakefulness and may disrupt non-REM sleep. The four cardinal symptoms are:

1. Excessive daytime sleepiness.
2. Cataplexy.
3. Hypnogogic or hypnopompic hallucinations.
4. Sleep paralysis.

Only 10–15% of patients with narcolepsy have all four features. An increasingly recognized feature is severely disrupted nocturnal sleep with frequent arousals and associated parasomnias, which may contribute to high levels of excessive daytime sleepiness.

Narcolepsy can be subdivided into two types, depending on the presence of cataplexy and associated hypocretin deficiency. Type 1 is diagnosed based on diagnostic sleep investigations (polysomnography and multiple sleep latency tests) in the presence of typical cataplexy or severe deficiency of CSF hypocretin levels. If sleep investigations are diagnostic in the absence of cataplexy or hypocretin deficiency, the disorder is labelled narcolepsy type 2.

Treatment and evidence base

Treatment for narcolepsy is tailored to the most troublesome symptoms reported by the subject. Usually this is excessive daytime sleepiness although cataplexy can be disabling and intrusive in a minority. Behavioural modifications such as strategic napping, judicious use of caffeine and formal sleep hygiene advice can be helpful. Most patients will also benefit from pharmacological treatment.

Excessive daytime sleepiness

- *First line*: armodafinil/modafinil.

- *Second line*: Stimulants such as dexamfetamine or methylphenidate.
- *Third line*: Sodium oxybate or pitolisant.

Stimulants

Armodafinil and modafinil are usually considered first line, in view of their robust efficacy data, favourable side-effect profile, and a low risk of tolerance. Amphetamine derivatives such as dexamfetamine and methylphenidate are useful second-line agents but are associated with vascular and psychiatric side effects.

Sodium oxybate and pitolisant

Sodium oxybate and pitolisant are newer agents effective in the management of both excessive daytime sleepiness and cataplexy. Some countries may require these to be used only when stimulants have failed due to their comparatively higher costs. Sodium oxybate is an effective agent but its use is complicated by the fact that it is the sodium salt of gamma-hydroxybutyrate (GHB) an agent abused in the context of sexual assault. As such extra precautions are taken to ensure it is used appropriately. In the UK, it is a schedule 2-controlled drug and in the USA, it is only available through risk evaluation mitigation strategy (REMS) programmes. Pitolisant is a histamine H3-receptor antagonist/inverse agonist. Its efficacy has been confirmed in several RCTs, the Epworth Sleepiness score reduced by 3 points compared to placebo ($p = 0.024$) and the mean weekly cataplexy rate reduced by 75% vs. 38% with placebo ($p < 0.0001$).[8]

Cataplexy and other REM-related symptoms (sleep paralysis and hallucinations)

These symptoms are commonly treated with antidepressant medications that are thought to suppress or inhibit REM sleep. Clomipramine, fluoxetine, and venlafaxine have been shown to be of benefit in small series only. The evidence base for this treatment is limited, despite being common clinical practice. Sodium oxybate and pitolisant have demonstrated efficacy in the context of RCTs but there are issues with regards to cost-effectiveness given their expense.

Circadian rhythm sleep–wake disorders

Circadian rhythm sleep–wake disorders are characterized by disruption of the normal timings of sleep and wakefulness. There are six categories recognized by the International Classification of Sleep Disorders. Delayed sleep phase syndrome, where sleep onset occurs substantially later than conventional sleep, is the commonest and can be mistaken for insomnia, especially in younger populations. There is evidence that use of melatonin is effective in jet lag disorder, delayed sleep phase syndrome, and non-24-h sleep rhythm disorder.

Treatment aims to realign the circadian rhythm with the conventional 24-h cycle, using a combination of behavioural interventions, melatonin and light-box therapy (phototherapy).

Non-REM parasomnias

Parasomnias are loosely defined as abnormal events occurring in association with sleep and are classified according to the sleep stage in which they occur.

The commonest are non-REM parasomnias, which are incomplete arousals from deep non-REM sleep and include night terrors, sleepwalking, and confusional arousals. They sometimes produce violent or goal-directed complex behaviour, particularly in adults.

Treatment

For the majority of patients, medical treatment is not required. The reassurance of a formal diagnosis and avoidance of potential triggers, such as sleep deprivation, caffeine, and alcohol are sufficient. A minority with frequent episodes, resulting in sleep disruption and excessive daytime sleepiness, or who present with injurious or dangerous behaviour may require medical treatment. Clonazepam, a long-acting benzodiazepine, or antidepressants, such as SSRIs fluoxetine, citalopram, and paroxetine, are most commonly used. Melatonin also helps some patients. These therapies probably work by reducing the number of arousals although the mechanism remains speculative. Evidence for their use comes from case series and clinical experience rather than RCTs.[9]

REM sleep behaviour disorder

During REM sleep, voluntary muscles are normally atonic. RBD is characterized by the loss of this atonia, resulting in dream enactment. RBD is associated with neurodegenerative conditions, most commonly Parkinson's disease (PD), and can predate the onset of extrapyramidal symptoms by many years. In younger patients, RBD may be seen in association with narcolepsy, treatment with antidepressant medications, or alternatively it may occur in isolation or together with non-REM parasomnia activity.

Treatment

- *First line*: Conservative measures including treating co-morbid sleep disorders, optimizing nocturnal akinesia in PD patients and ensuring there are no sharp objects around the bed space.
- *Second line*: Melatonin 2–10 mg OD, clonazepam 0.5–2 mg ON or zopiclone 3.75–7.5 mg ON.

Evidence base

When treatment is indicated, clonazepam is often effective but can produce daytime sedation and exacerbate sleep-related breathing disorders such as obstructive sleep apnoea.[10] Zopiclone was found to be effective in a small study.[11] Prolonged-release melatonin, often at relatively high doses of 5–10 mg nocte, has been shown to be effective in small case series. A more recent small RCT of RBD, however, produced a negative result when 30 patients with PD and RBD were randomized to 4 mg prolonged-release melatonin or placebo. There was no difference in RBD events or side-effect profile over an 8-week trial.[12]

Restless legs syndrome

Restless legs syndrome (RLS) is characterized by the description of sensory discomfort or paraesthesia in the limbs resulting in the need to move them around. Symptoms are worst at rest and in the evening or when trying to sleep at night. Patients experience at least partial relief with motor activity, often getting out of bed at night to move around. This can severely affect sleep quality and often results in insomnia. An autosomal dominant-like inheritance is noted in a significant proportion of cases, especially if onset is at an early age.

Risk factors for RLS should be identified and treated where possible, including:

- Iron deficiency.
- Chronic renal disease (especially those on dialysis).
- Peripheral neuropathy (vitamin B_{12} and folic acid deficiency, especially in older individuals or pregnant women).
- PD.
- Pregnancy.

Treatment

The need for treatment should be based on the frequency of troublesome symptoms and their effect on sleep quality. For patients with infrequent bouts of RLS, treatment as required may be appropriate. Avoidance of aggravating substances, such as nicotine, caffeine, and alcohol, should be advised. Stretching and light exercise may also help. The following pharmacological approaches are recommended if non-drug treatments fail:

- *First line*: non-ergot dopamine agonists (DAs) (e.g. pramipexole, ropinirole, and rotigotine); $\alpha 2\delta$ ligands (gabapentin enacarbil, gabapentin, or pregabalin).

Although the doses of DAs are lower than those used for PD, impulse control disorders are a significant risk in RLS, affecting 6–17% of patients overall. Patients should be warned or even specifically consented for this, and their use avoided in patients with problems with addiction.
Co-morbid anxiety, insomnia, substance abuse and pain favours use of $\alpha 2\delta$ ligands, whilst obesity and OSA favour the use of DAs.

- *Second line*: Opiates such as codeine or benzodiazepines as a short-term measure can be helpful if patients have severe episodes of symptoms.
- Additionally, iron supplementation in those known to be deficient can improve symptoms. Guidelines vary but ferritin should be replaced if levels are lower than 50–75 micrograms/L. Oral ferrous sulphate at 200 mg OD or on alternate days if poorly tolerated is typically sufficient and is less likely to cause constipation as a side effect than higher doses. Co-prescription of vitamin C can increase absorption. Other formulations including those given intravenously can also be tried if standard preparations are not tolerated.

Evidence base

Dopamine agonists

Pramipexole, ropinirole, and transdermal rotigotine have been shown to be effective in RCTs for the short- and long-term treatment of RLS. Their longer half-lives and lower incidence of augmentation mean that they are preferred to levodopa as first-line treatment. Of the DAs, rotigotine appears to be associated with the lowest incidence of augmentation (13%).[13]

$\alpha2\delta$ ligands

Gabapentin enacarbil, gabapentin, and pregabalin have all have been shown to be effective and well tolerated in treating RLS,[14] with the strongest evidence for gabapentin enacarbil (the only agent licensed for this indication).[15] This is a prodrug of gabapentin with greater bioavailability. These agents may be of particular use in patients with co-morbid neuropathic pain.

Levodopa

Due to the significant risk of augmentation with levodopa (in particular at doses >200 mg/day), it is now mainly used in diagnosis of RLS and for patients requiring intermittent treatment. A Cochrane review of nine RCTs investigating the use of levodopa in moderate to severe RLS found that it improved symptoms, sleep, and clinician ratings, compared to placebo.[16] Active comparison trials between levodopa and DAs suggest that DAs may be better at controlling RLS symptoms and improving quality of life; however, confidence intervals were large, meaning that firm conclusions could not be made.

Opioids and benzodiazepines

Opioids may be effective where other treatments have failed; however, their potential for abuse and side-effect profile should be considered before use. Short-term benzodiazepines may also be useful to improve quality of sleep in refractory cases.

Augmentation

70% of patients treated with levodopa, and to a lesser extent DAs, develop the phenomenon of 'augmentation' wherein symptoms occur earlier in the day and spread to the trunk and upper limbs with reduced duration of treatment effect. This can be difficult to manage but only occurs with dopaminergic agents (and tramadol, which has some action on dopaminergic receptors).

The risks can be minimized by avoiding dopaminergic agents, managing risk factors for RLS and, if dopaminergic agents are required, preferentially using agents with a long half-life.

If augmentation occurs, management depends on symptom severity. If mild, the dose can be slightly up titrated or split to cover a longer period. If severe, then cross-titration to gabapentin enacarbil, gabapentin or pregabalin is preferred. Alternatively, the medication can be switched to a longer acting dopaminergic agonist such as rotigotine. Short courses of opiates including long-acting opiates such as methadone can also help in the cross-titration period. Intravenous iron infusions are also sometimes considered based on reports from case series.

Periodic limb movements of sleep

PLMS are repetitive, stereotyped limb movements that occur every 5–90 s during sleep. If they result in arousal and sleep-maintenance insomnia, with consequent excessive daytime sleepiness, the term periodic limb movement disorder (PLMD) can be used. There is a strong association with RLS, which may contribute to insomnia and daytime sleepiness.

Treatment

Clinical trials have mainly been performed for RLS, but it appears that PLMD will often respond to the same medications. Iron deficiency can exacerbate both RLS and PLMS, and iron supplementation should be given if ferritin levels are below 50–75 micrograms/L. Potential triggers, such as alcohol, nicotine, and caffeine, should be avoided. Otherwise, selection of medication is the same as for RLS.

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Chapter 18

Neurological infections

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Introduction

This chapter considers the common neurological infections and the drugs available to treat them. Due to constraints of space and the knowledge that, for the less commonly used antimicrobials, guidance will be provided by infectious disease specialists, the majority of antimicrobials do not have individual drug monographs.

Pathophysiology

A wide variety of microorganisms target different components of the nervous system. In the central nervous system (CNS), this may result in isolated infection of the brain parenchyma (encephalitis), the meninges (meningitis), or the spinal cord (myelitis). Some of the organisms which cause encephalitis also cause an associated meningeal reaction or spinal cord inflammation, and these terms may be used alone or in various combinations to reflect what part of the neuroaxis is involved, e.g. meningoencephalitis, encephalomyelitis. Furthermore, infection may spread into the CNS from adjacent sites (parameningeal infections such as brain abscess, subdural empyema) or from the blood (endocarditis, septicaemia). Infection of components of the peripheral nervous system (PNS) is relatively uncommon. Special consideration needs to be given to neurological infections in the immunocompromised, as opportunistic infection by a different range of microorganisms commonly occurs.

Meningitis

Meningitis is the commonest CNS infection. In the UK, the majority of cases are self-limiting viral infections. However, differentiation between bacterial and viral meningitis on history alone is unreliable. CSF examination is helpful to distinguish between viral and bacterial meningitis, and may suggest other causes (see Table 18.1).

Table 18.1 Typical CSF findings in CNS infections

	Viral meningo-encephalitis	Community-acquired bacterial meningitis	Tuberculous meningitis	Fungal	Normal
Opening pressure	Normal/high	High	High	High to very high	10–20 cmH_2O
Colour	Clear	Cloudy	Cloudy/yellow	Clear/cloudy	Clear
Cells (cells/μL)	5–1000	100–50 000	25–500	0–1000	<5
Differential	Lymphocyte	Neutrophil	Lymphocyte	Lymphocyte	Lymphocyte
CSF:plasma glucose	Normal	Low	Low to very low (<30%)	Normal to low	66%
Protein (g/L)	0.5–1	>1	1.0–5.0	0.2–5.0	<0.45

Community-acquired bacterial meningitis

The 'big three' microorganisms responsible for acute bacterial meningitis are *Streptococcus pneumoniae, Neisseria meningitides*, and *Haemophilus influenzae. Listeria monocytogenes* should be considered in the elderly or immunosuppressed.[1] Empirical therapy with both antibacterials and antivirals is often advised[2] (see Tables 18.2 and 18.3). In most settings, a third-generation cephalosporin and aciclovir are used, but meropenem or chloramphenicol are advised if there are concerns about penicillin allergy. Amoxicillin can be added if *L. monocytogenes* is suspected, and vancomycin added if penicillin-resistant pneumococci are suspected. The duration of antimicrobial therapy is usually 10–14 days.

Table 18.2 Empirical therapy in suspected community-acquired bacterial meningitis

Patient group	Common organisms	Initial IV antibiotics
Age 2–50 years	N. *meningitides* and *S. pneumoniae*	Third-generation cephalosporin ± vancomycin
Age >50 years	N. *meningitides,* *S. pneumoniae*, and *L. monocytogenes*	Third-generation cephalosporin ± amoxicillin ± vancomycin
Immunocompromised	N. *meningitides,* *S. pneumoniae,* *L. monocytogenes*, and Gram-negative bacilli	Third-generation cephalosporin, and amoxicillin ± vancomycin

Table 18.3 General recommendations for IV empirical antibiotic treatment doses

Treatment		Dose
Third-generation cephalosporin	Cefepime	2 g every 8 h
	Cefotaxime	2 g every 4–6 h
	Ceftazidime	2 g every 8 h
	Ceftriaxone	2 g every 12 h
Amoxicillin or ampicillin		2 g every 4 h
Chloramphenicol		1–1.5 g every 6 h
Meropenem		2 g every 8 h
Vancomycin		15 mg/kg every 12 h

Adjunctive steroids

Use of steroids in bacterial meningitis remains controversial.[3,4] Adjunctive dexamethasone is thought to confer benefit, particularly in treatment of *H. influenzae* and *S. pneumoniae* meningitis. A large randomized trial of dexamethasone (10 mg IV 15–20 min before or with the first dose of antibiotic, then 6-hourly for 4 days) in adults with acute bacterial meningitis reduced the chance of an unfavourable outcome from 25% to 15% and mortality from 15% to 7%. The benefits were most striking in patients with pneumococcal meningitis.

Complications of acute bacterial meningitis

Patients with acute bacterial meningitis are at risk of various neurological and systemic complications and thus need intensive monitoring. Systemic complications of hypotension, septic shock, and adult respiratory distress are predictors of poor outcome. Hyponatraemia (serum sodium <135 mmol/L) is found in 30% of patients. Hypernatraemia (serum sodium >143) occurs in 7% of patients, more commonly in those with severe disease, and is an independent predictor of poor outcome and mortality. Cerebral oedema, hydrocephalus (either communicating or obstructive), cerebral infarction from septic venous thrombosis or endarteritis, and seizures are the major neurological complications seen.

Chemoprophylaxis of acute bacterial meningitis

Chemoprophylaxis is indicated for close contacts of meningococcal meningitis cases and for patients with meningococcal meningitis treated with penicillin or amoxicillin monotherapy, as carriage is not reliably eradicated by these agents. Rifampicin 600 mg bd PO for 2 days, ceftriaxone 250 mg stat IM dose, ciprofloxacin 500 mg stat PO dose, or azithromycin 500 mg stat PO dose are believed to be equally effective.

Chronic meningitis

Chronic meningitis is defined as meningeal inflammation, diagnosed clinically and with supporting CSF findings, persisting for at least 4 weeks. Infections account for a proportion of cases (see Table 18.4), but neoplastic and other aseptic disorders should also be considered, and no cause is identified in up to a third of cases.

Table 18.4 Infective causes of chronic meningitis

Bacteria	Partially treated bacterial meningitis
	Tuberculosis (TB)
	Syphilis
	Lyme disease
	Other: *Brucella, Leptospira, Listeria, Mycoplasma*
Viral	HIV
	Herpesviruses: HSV, EBV
	Subacute sclerosing panencephalitis (measles)
Fungal	Blastomycosis, *Candida*, coccidiomycosis, cryptococcus, and histoplasmosis
Protozoa and metazoa	Acanthamoeba, *Angiostrongylus*, parasitic worms, and toxoplasmosis
Others that mimic chronic meningitis	Endocarditis/other embolic foci
	Parameningeal infection, e.g. epidural abscess/sinusitis

Tuberculosis

TB typically affects the CNS in three ways: TB meningitis, intracerebral tuberculomas, and spinal TB. Treatment requires combination therapy: rifampicin, isoniazid, pyrazinamide, and either ethambutol or streptomycin.[5] Pyridoxine must be co-prescribed to prevent peripheral neuropathy due to isoniazid. Small trials indicate that clinical outcomes might be improved with increased doses of rifampicin, the addition of linezolid or fluoroquinolones to standard antituberculosis therapy, or treatment with adjunctive aspirin combined with corticosteroids. Large phase 3 clinical trials are underway worldwide to address these.[6,7] Treatment is for a minimum of 12 months, administered in conjunction with corticosteroids for the first 6–8 weeks in HIV-negative patients.[8]

Encephalitis and myelitis

Encephalitis and myelitis may arise from post-infectious or post-vaccination autoimmune processes, as well as from direct infection of the parenchyma.

Acute encephalitis

Encephalitis means inflammation of the brain parenchyma and typically presents with a febrile illness, severe headache, nausea and vomiting, and reduced consciousness, often with seizures and focal neurological signs. Encephalitis can be caused by a range of viruses, the herpesviruses and arthropod-borne (arbo-) viruses being the most important (see Table 18.5). Other microorganisms can also cause encephalitis, particularly protozoa, such as *Toxoplasma gondii*, and bacteria, including *L. monocytogenes* and *M. tuberculosis* (see Table 18.6).

Table 18.5 Causes of acute viral encephalitis

SPORADIC	
Herpesviruses	HSV 1 and 2, VZV, EBV, cytomegalovirus (CMV), human herpesvirus (HHV) 6 and 7
Enteroviruses	Coxsackie viruses, echoviruses, enteroviruses, parechovirus, and poliovirus
Paramyxoviruses	Measles and mumps
Others (rare)	Adenovirus, influenza viruses, lymphocytic choriomeningitis virus, parvovirus, and rubella
GEOGRAPHICALLY RESTRICTED (mostly arboviruses)	
Africa	Rabies and West Nile
Asia	Dengue, Japanese encephalitis, Murray Valley encephalitis, rabies, and West Nile
Australasia	Japanese encephalitis and Murray Valley encephalitis
Europe/Middle East	Rabies, tick-borne encephalitis, and Tosana
The Americas	Dengue, Eastern and Western equine encephalitis, rabies, St Louis, and West Nile

Table 18.6 Other infectious causes of encephalitis

Bacteria	Actinomycosis, bacterial meningitis, *Brucella*, cat scratch fever, erlichiosis, *Leptospira, Listeria*, Lyme disease, *Mycoplasma, Nocardia*, relapsing fever, Rocky Mountain spotted fever, Q fever, syphilis, TB, typhoid fever, typhus, and Whipple's disease
Fungi	Candidiasis, coccidioidomycosis, *Cryptococcus*, histoplasmosis, and North American blastomycosis
Parasites	Amoebiasis, cerebral malaria, cystericosis, *Echinococcus*, toxoplasmosis, trichinosis, and trypanosomiasis

As a significant proportion of infectious encephalitis in the UK and USA is caused by herpesviruses, aciclovir is the treatment of choice.[9] It is usually commenced if the initial CSF and/or radiological investigations are suggestive of viral encephalitis. However, if a delay of ≥6 h is likely before an LP can be done or if the patient is deteriorating, it should be started empirically. In confirmed diagnoses, treatment is for 14–21 days or longer if the CSF viral polymerase chain reaction (PCR) remains positive. Steroids may be beneficial in the management of varicella-zoster virus (VZV) encephalitis, but their use in HSV encephalitis remains unclear following investigation in a large multicentre trial which was stopped early due to slow recruitment.[10]

Myelitis

Commonly, myelitis is a primary or post-infectious autoimmune phenomenon, but occasionally direct infection can be the cause, in which case organisms to consider include viruses (VZV, HSV, CMV, EBV, West Nile, influenza, echovirus, HIV, hepatitis A, rubella, measles), *Mycoplasma*, Lyme disease, syphilis, and parasites.

Lyme disease

Manifestations of neuroborreliosis (*Borrelia burgdorferi*) include encephalitis, myelitis, and cerebral vasculitis and should be treated with IV ceftriaxone. Lyme disease may also cause optic neuropathies, painful radiculoneuritis, often affecting the upper trunk and back which may resemble acute inflammatory demyelinating polyneuropathy (AIDP) or a plexopathy (Bannwarth's syndrome), or cranial nerve palsies, treated with PO doxycycline. There may be a late mild chronic polyradiculoneuropathy, with or without acrodermatitis chronica atrophicans (a characteristic progressive fibrosing skin rash caused by ongoing active infection). Guidance varies but typically early neuroborreliosis (symptoms present for ≤6 months) is treated for 14 days, and late neuroborreliosis for 21 days.[11,12]

SARS-CoV-19

SARS-CoV-2 infection is associated with a wide spectrum of neurological syndromes affecting the whole neuraxis, including the cerebral vasculature and, in some cases, responding to immunotherapies.[13]

The most common neurological symptoms related to acute infection include smell and taste disorders, headache, and myalgia.

More severe complications include encephalopathies with delirium/psychosis but no distinct MRI or CSF abnormalities, and inflammatory CNS syndromes including encephalitis, ADEM with a relatively high incidence of haemorrhagic change, and myelitis.

Treatment of inflammatory CNS syndromes with a high dosage (1–2 g/24 h) intravenous corticosteroids for 3–5 days, followed by oral tapering is recommended, with IVIg (0.4 g/kg body weight) if there is an inadequate response to corticosteroids.

Other important complications of SARS-CoV-19 include ischaemic strokes associated with a pro-thrombotic state/pulmonary thromboembolism, CVST, and neuromuscular diseases, chiefly Guillain–Barré syndrome, brachial plexopathy, and myopathy with elevated CK levels. Treatment is generally tailored to the specific neurological syndrome.

Exacerbation of pre-existing neurological conditions, notably MS and myasthenia is a recognized phenomenon. In addition to older age, Afro-Caribbean and Asian ethnicity and co-morbidities of diabetes, cardiovascular, and respiratory disease, susceptibility to more severe Covid infection is seen with Parkinson's disease, Alzheimer's disease, and patients with MS treated with CD20 therapies.

Covid vaccination with the AstraZeneca/Oxford vaccine (ChAdOx1 nCoV-19) was associated with CVST and thrombocytopenia but no other Covid vaccine-specific syndromes have been described.

Post Covid-19 neurological syndrome/long Covid

Long covid is a constellation of symptoms that may persist after covid infection or may occur several weeks after infection and continue for months. It is characterized by combinations of dyspnoea, cough, fatigue, brain fog, mood disorder, sleep disturbance, pain syndromes, and smell and taste dysfunction. The pathophysiology remains unclear and treatment is symptomatic.

Brain abscesses and parameningeal infections

Brain abscesses

Brain abscesses arise by two main routes: local spread (from sinusitis, otitis media, mastoiditis, dental sepsis, penetrating head injury, or neurosurgery) or haematogenous spread (from valvular heart disease with right-to-left shunt, pulmonary arteriovenous fistula in hereditary haemorrhagic telangiectasia, suppurative pulmonary infection, or endocarditis). The most common causative microorganisms are streptococci, staphylococci, and anaerobes. In immunosuppressed individuals, opportunistic infection should also be considered.

Treatment

Empirical treatment is guided by the likely source of infection. Given the frequency of anaerobic organisms, metronidazole plays a key role.[14,15] Treatment is usually for a minimum of 4–6 weeks and depends upon whether the abscess has been excised, aspirated, or managed solely with antibiotics. Duration can be guided by serum CRP measurements, with switch from parenteral to oral therapy once clinical improvement occurs and the CRP has begun to fall.

Subdural empyema

Subdural empyemas usually arise by local spread from frontal sinusitis, otitis media ± mastoiditis. Spread tends to be faster, and mortality is consequently high, ranging from 6% to 20%. The commonest organisms vary with initial site of infection, but are typically staphylococci or streptococci.

Epidural abscess

Spinal epidural abscesses usually arise from vertebral osteomyelitis or discitis, but other causes include spinal surgery or spinal anaesthesia, drug use, or local trauma. Intracranial epidural abscesses can also occur. In 60% of cases, the responsible organism is *S. aureus*, but Gram-negative anaerobic rods, streptococci, and *M. tuberculosis* are occasionally implicated.

Septic intracranial sinus thrombosis

Septic cavernous sinus thrombosis, and lateral or sagittal sinus thrombosis arise from facial infections in 50% of cases, sphenoid sinusitis in 30%, dental infection in 10%, and occasionally from otitis media, mastoiditis, or other local infections. Diabetes mellitus is a significant risk factor.

Neurological infections in the immunocompromised

Patients with compromised immune systems are prone to a range of opportunistic infections not commonly seen in immunocompetent patients. A wide variety of microorganisms can cause opportunistic infections, most commonly viruses and fungi, but occasionally bacteria and protozoa. Those of most relevance to clinicians in developed countries are summarized in Table 18.7.

Table 18.7 Opportunistic neurological infections in the immunosuppressed

Organism	Clinical syndrome	Treatment
Viruses		
CMV	Encephalomyelitis, brainstem encephalitis, radiculitis, retinitis	Highly active antiretroviral therapy (HAART) for HIV, ganciclovir, foscarnet, cidofovir

Table 18.7 (*Contd.*)

Organism	Clinical syndrome	Treatment
JC virus	PML in HIV, transplant recipients, natalizumab treatment for MS, other biological agents	No known treatment Responds to immune reconstitution in MS (PLEX to remove natalizumab), and HAART for HIV but not usually in immunosuppressed transplant recipients
HIV	HIV encephalopathy	HAART
VZV	Reactivation—shingles, post-herpetic neuralgia, myelitis, meningoencephalitis, vasculopathy with stroke, cranial neuropathies, cerebellitis	Aciclovir, famciclovir
Fungi	See Table 18.8	
Protozoa		
Toxoplasma	Commonly presents with headache, fever, and neurological deficit associated with multifocal lesions, less commonly as unifocal lesions or as an encephalitic syndrome	Sulfadiazine plus pyrimethamine, or clindamycin plus pyrimethamine
Acanthamoeba spp (*Naegleria fowleri, Balamuthia mandrillaris*)	Granulomatous amoebic meningoencephalitis (freshwater swimming)	Amphotericin B, rifampicin, fluconazole
Bacteria		
M. *tuberculosis*	Meningitis, brain abscess, spinal epidural abscess	Quadruple anti-TB therapy plus corticosteroids
L. *monocytogenes*	Meningitis, brainstem encephalitis	High-dose amoxicillin
Nocardia	CNS infection, brain abscess	Meropenem
Treponema pallidum[16,17]	Neurosyphilis—meninges, brain, brainstem, spinal cord, nerve roots, and cerebral and spinal blood vessels	IV benzylpenicillin, or IM procaine benzyl penicillin plus probenecid od

Fungal infections

Risk factors include immunocompromise of any cause and living in endemic areas. Fungal pathogens encountered in the CNS include yeasts (*Candida, Cryptococcus*), moniliaceous moulds (*Aspergillus* spp., *Fusarium* spp.), dimorphic fungi (*Blastomyces, Coccidioides, Histoplasma*), and zygomycetes (*Mucor* spp., *Rhizopus* spp.). CNS infection occurs through haematogenous spread, CSF seeding, or direct extension. Untreated, these are rapidly fatal infections, and mortality is high, even with early aggressive treatment.

See Table 18.8 for typical clinical presentations and treatments of the more common fungal CNS infections.

Table 18.8 Fungal infections of the CNS

Organism	Clinical	Treatment
Coccidioides	Meningitis with basal cistern enhancement	Fluconazole
Candida	Meningitis in the immunosuppressed, organ transplant recipients, or patients following neurosurgery, especially if with prosthesis. Numerous microabscesses on MRI	Amphotericin B plus flucytosine Fluconazole, posaconazole
Aspergillosis	Rhinocerebral infections, especially in diabetics, immunosuppressed Angioinvasive—multifocal haemorrhagic infarcts, cavernous sinus thrombosis	Surgical debridement High-dose amphotericin B Posaconazole, voriconazole
Cryptococcus neoformans	Cryptococcal meningitis in immunosuppressed, often with raised ICP Rarely focal signs from cryptococcoma Gelatinous pseudocysts in basal ganglia on MRI	In HIV—flucytosine plus amphotericin induction, then fluconazole maintenance
Mucormycosis	Invasive and highly aggressive, with high mortality. Often rhino-orbital sinus infection, frontal lobe lesions, cavernous sinus lesions Risk factors: diabetes (diabetic ketoacidosis), neutropenia, malnutrition, iron overload in dialysis, IV drug users	Amphotericin B, posaconazole

Parasitic infections

Parasitic CNS infections are relatively common worldwide but rarely encountered in clinical practice in the UK, Europe, and the USA. The typical clinical presentations and treatment of the more common CNS parasites are briefly outlined in Table 18.9.

Table 18.9 Parasitic infections of the CNS

Organism	Clinical syndrome	Treatment
Schistosomiasis[18,19]	Cerebral disease (*Schistosoma japonicum*), myelopathy (*Schistosoma mansoni* and *Schistosoma haematobium*) Early infection asymptomatic or acute encephalitis/myelitis (Katayama fever)	Praziquantel Corticosteroids for Katayama fever
Trypanosomiasis	American trypanosomiasis (Chagas' disease, *Trypanosoma cruzi*)—acute meningoencephalitis West and East African trypanosomiasis (sleeping sickness, *Trypanosoma brucei*)—encephalopathy with headache and prominent somnolence	Nifurtimox, benznidazole Suramin, melarsoprol, pentamidine, eflornithine
Plasmodium spp.	Cerebral malaria—rigors, fever, encephalopathy with raised ICP, delirium, seizures, focal neurological signs, and coma	*Plasmodium falciparum*—IM or IV artesunate plus doxycycline (IV quinine is an alternative to artesunate if the latter is not available)
Toxoplasma	Single or multiple brain lesions	Sulfadiazine, pyrimethamine, and folic acid Co-trimoxazole Clindamycin
Cysticercosis[20]	Multiple parenchymal, intraventricular, or subarachnoid (racemose) cysts—epilepsy, headache, hydrocephalus, stroke, neuropsychiatric symptoms Vasculitis, arachnoiditis, encephalitis	Albendazole ± corticosteroids. Anticonvulsants

Bacterial neurotoxins

In the developed world, botulism and tetanus are rare, but important, causes of neuromuscular disease. Both result from the production of neurotoxins by clostridial species—*Clostridium botulinum* and *Clostridium tetani*, respectively.

Botulism

Botulism is an important differential for flaccid paralysis and is commonly mistaken for AIDP or myaesthenia gravis (MG). Botulinum toxin acts at the neuromuscular junction (NMJ), preventing acetylcholine release. Botulism is characterized by progressive descending weakness, typically affecting the cranial nerves, without associated sensory involvement. In adults, the two main routes of exposure are ingestion of contaminated food and via wounds (including 'skin popping'). Diagnosis is by identification of toxins in serum or faeces. Wound swabs, faecal samples, and suspected food products should also be cultured for *C. botulinum* bacteria. Management should be undertaken in an intensive care unit (ICU), as respiratory paralysis is common. Antibiotics (IV or IM benzylpenicillin 2.4–4.8 g/day in divided doses every 6 h; in penicillin-allergic patients, use IV metronidazole 500 mg every 8 h for 7 days), in addition to wound debridement, should be used in the management of wound-acquired botulism but avoided in food-borne disease due to concerns of bacterial cell rupture and release of more neurotoxin. In food-borne disease, laxatives, enemas, and, if caught early enough, gastric lavage have been tried to reduce gastrointestinal levels of neurotoxin. IV botulinum antitoxin should be administered as soon as possible.[21]

Tetanus

Tetanus is caused by a toxin secreted by wound-borne *C. tetani*, which binds peripheral nerve terminals and is subsequently transmitted to the CNS where it blocks the release of inhibitory neurotransmitters GABA and glycine. This results in spasms, commonly of the jaw (trismus), which may subsequently spread to other striated muscle groups, leading to sustained contraction. Autonomic dysfunction and respiratory failure occur in severe disease. Diagnosis is predominantly clinical, as wound culture for *C. tetani* has low sensitivity. Reported case fatality varies but can be as high as 80%. Treatment requires a combination of disease-specific therapy and supportive measures. The antitoxin and appropriate antibiotics, usually a combination of metronidazole and penicillin, should be administered as soon as possible. Adequate wound debridement is essential. Benzodiazepines ± magnesium sulfate are used to control muscle spasm, and sympathetic overactivity may require both α- and β-blockade.[22]

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Chapter 19

Metabolic disorders

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Introduction

Metabolic disorders with neurological involvement can be divided into three broad categories: inborn errors of metabolism, acquired nutritional deficiencies, and neuro-metabolic disorders due to toxins or drugs.

Inborn errors of metabolism

The conditions discussed in this chapter are those most commonly encountered in adult neurology practice and/or are amenable to specific treatments. A typical classification is given in Table 19.1.[1]

Table 19.1 Neuro-anatomic classification of inherited neuro-metabolic disorders

Distribution of pathology	Disorders
Poliodystrophies (cortical grey matter: myoclonus, seizures, dementia, retinopathy)	Neuronal ceroid lipofuscinoses, GM2 gangliosidosis (Tay–Sachs), mucopolysaccharidoses (MPS), Gaucher's, Niemann–Pick
Leukodystrophies (white matter: spasticity ± ataxia, optic atrophy, cortical blindness, deafness)	Adrenoleukodystrophy (ALD), metachromatic leukodystrophy (MLD), Pelizaeus–Merzbacher, globoid cell dystrophy (Krabbe), phenylketonuria with dysmyelination
Corencephalopathies (deep telencephalon, diencephalon, and mesencephalon: movement disorders)	Wilson's disease, Huntington's disease
Spinocerebellopathies (spinal cord, cerebellum, pons, medulla: spasticity, ataxia)	Hereditary spastic paraplegias, Friedreich's ataxia, spinocerebellar ataxia (SCA), olivopontocerebellar atrophy
Diffuse encephalopathies	Hyperammonias, lactic acidaemias, homocysteinuria
Metabolic myopathies (muscle: rhabdomyolysis, exercise-induced myalgia, cramps, muscle weakness)	Acid maltase deficiency (Pompe), phosphofructokinase (PFK) deficiency, myophosphorylase deficiency (McArdle's)
Metabolic peripheral neuropathies (peripheral nerve: distal weakness and paraesthesiae)	Fabry disease, porphyria, SCA

Lysosomal storage disorders

In lysosomal storage disorders (LSD), deficiencies of specific enzymes cause the accumulation of non-degraded macromolecules within lysosomes that ultimately cause pathological changes to normal cell biology. The clinical phenotype of each disorder depends on which tissues have the highest turnover of accumulated macromolecule and consequently LSDs can produce a variety of different neuro-anatomic phenotypes (see Tables 19.1 and 19.2). To date, enzyme replacement therapy (ERT) has been approved worldwide for eight lysosomal storage diseases: Gaucher's disease; Fabry disease; mucopolysaccharidoses types I, II, IVA, VI and VII; and Pompe disease.

Gaucher's disease

Gaucher's disease (glucosylceramide lipidosis) is the most prevalent of the LSDs, affecting 1 in 50 000 of the population worldwide, but 1 in 800 individuals of Ashkenazi Jewish descent. The primary metabolic defect is a deficiency of glucocerebrosidase (also known as acid β-glucosidase), which leads to accumulation of glucocerebroside (glucosylceramide) within lysosomes. Lipid-laden macrophages, Gaucher's cells, are stored throughout

Table 19.2 Deficient Enzymes in Lysosomal Storage Disorders

Lysosomal storage disorders		Deficient enzyme
Sphingolipidoses		
	GM1 gangliosidoses	β-galactosidase
	GM2 gangliosidoses (Tay Sachs disease)	hexaminidase A
	Niemann-Pick disease	sphingomyelinase
	Globoid cell leukodystrophy (Krabbe disease)	galactocerebrosidase
	Metachromatic leukodystrophy	arylsulphatase A
	Gaucher disease	glucocerebrosidase
Mucopolysaccharidoses		glycosaminoglycan cleaving enzymes
Glycoproteinoses		glycoprotein cleaving enzymes
Glycogenosis type II (Pompe disease)		α-glucosidase
Neuronal ceroid lipofuscinosis		lysosomal proteases

the reticuloendothelial system and are useful in diagnosis. Diagnosis is confirmed by measurement of white cell glucocerebrosidase levels.

Several phenotypes are described, Type I (adult non-neuronopathic), Type II (acute infantile neuronopathic) and Type III chronic/subacute juvenile neuronopathic. Type IIIA (chronic neuronopathic form) may present in adulthood with slowly progressive neurological deterioration, with the hallmark supranuclear horizontal gaze palsy, progressive myoclonic encephalopathy with seizures and dementia, and variable ataxia8 spasticity.

Treatment

ERT with recombinant human glucocerebrosidase (imiglucerase, velglucerase alfa, taliglucerase alfa), and substrate reduction therapies (miglustat, eliglustat) are effective for treating systemic manifestations and are licensed for treating type I Gaucher and visceral type III Gaucher disease. However, there is no evidence that ERT reverses or slows the progression of neurological involvement. Haematopoietic stem cell transplantation may have a role in neuronopathic Gaucher's disease before neurological manifestations occur, and gene therapies are in development.[2,3]

Fabry/Anderson–Fabry disease

Fabry disease is the commonest lysosomal storage disease, after Gaucher's disease, affecting ~1 in 100 000 of the population and 1 in 40 000 males. It is transmitted by X-linked recessive inheritance. Reduced activity and misfolding of α-galactosidase A (α-Gal A) leads to accumulation of globotriaosylceramide in endothelial, vascular smooth muscle, and other cells, with multisystem consequences. The typical clinical picture is a 'bathing trunk' purpuric rash (angiokeratoma corporis diffusum) developing during childhood or adolescence. A painful sensory small-fibre peripheral neuropathy with or without autonomic features is common in childhood or early adult life. Renal failure, strokes, cardiovascular disease, or hypertrophic cardiomyopathy can occur, generally by middle age. Life expectancy is typically reduced by 20 years.

Treatment

Management includes symptom relief for neuropathic pain, optimization of vascular risk factors, renal transplant for renal failure, ERT, and oral chaperone therapy. Two different ERT products are available: Replagal® (agalsidase alfa) and Fabrazyme® (agalsidase beta). ERT may be combined with oral chaperone therapy (migalastat) which binds to the active site of α-Gal A and corrects misfolding of the enzyme.[4]

Evidence base

Limited data are available on the effect of ERT on disease progression and survival. A meta-analysis of six studies[5] showed that ERT did not prevent the development of cerebral white matter lesions but did reduce the rate of increase in left ventricular mass and the risk of end-organ complications (stroke, cardiac, or renal complications and death). The latest review from the Cochrane database[6] concluded that agalsidase beta is associated with a significantly lower incidence of renal, cardiovascular, and cerebrovascular events than no ERT, and to a significantly lower incidence of cerebrovascular events than agalsidase alfa.

Mucopolysaccharidoses

The mucopolysaccharidoses are a group of rare inherited disorders caused by specific lysosomal enzyme deficiencies, resulting in accumulation of incompletely degraded mucopolysaccharides in the cornea, cartilage, connective tissue, and reticuloendothelial system. There are seven subtypes, and all exhibit some period of normal development, followed by gradual decline of visceral, skeletal, and neurological function, the latter commonly including neurodevelopmental delay, cognitive and behavioural decline, seizures, sleep disorders, and optic neuropathy. There may also be high cervical cord compression from atlanto-axial instability and odontoid dysplasia, communicating hydrocephalus, and carpal tunnel syndrome. Diagnosis is made by detection of elevated urinary glycosaminoglycans (GAGs) and analysis of white cell enzymes.

Treatment

ERT is currently available for MPS types I, II, IVA, VI, and VII but is of limited efficacy and does not appear to impact CNS involvement.[7] Haematopoietic stem cell transplantation has been used successfully in type I and is under investigation for the other types. Substrate reduction and gene therapies are in early development.

Acid maltase deficiency (Pompe)

An autosomal recessive disease caused by deficiency of acid maltase (acid α-glucosidase), a lysosomal enzyme found in the CNS and skeletal muscle, which is involved in the conversion of maltose to glycogen. With the advent of newborn screening, prevalence is higher than originally thought and ranges between 1 in 4500 and 1 in 37000. There are four clinical phenotypes, distinguished by age at onset: infantile, late infantile, juvenile, and adult. The later-onset forms (LOPD) present as motor developmental delay and/or progressive myopathy, often with prominent cardiorespiratory involvement. Visceromegaly is common in younger cases. Diagnosis is with dry blood spot enzyme assay and genetic analysis but there is a role for muscle MRI, and muscle biopsy shows characteristic vacuolar changes with glycogen storage and increase acid phosphatase reactivity.

Treatment

ERT with alglucosidase alfa (Lymizyme® or Myozyme®) is effective, well tolerated, and attenuates progression in infantile onset (IOPD) and LOPD.[8] Two-thirds of patients stabilize or demonstrate improvement in creatine kinase (CK) levels and muscular and/or respiratory function on treatment. However, typically mild to moderate initial clinical improvement is followed by a plateau and then later mild decline.[9] Avalglucosidase alfa demonstrated superior efficacy to alglucosidase alfa and was Food and Drug Administration (FDA) approved in 2021, and the combination of cipaglucosidase with miglustat (small molecule chaperone which corrects protein misfolding and normalizes trafficking) was recently approved in light of increased efficacy compared with avalglucosidase alfa.[10] Adenoviral and lentiviral gene therapy shows promising results in animal studies and is under development.

Peroxisomal disorders

Peroxisomes are cell organelles that are mainly involved in lipid metabolism and are responsible for the synthesis of β-oxidase very-long-chain fatty acids (VLCFAs). They play an important role in early myelination and neuronal migration.

Adrenoleukodystrophy/adrenomyeloneuropathy

This is the most common peroxisomal disorder, with an incidence between 1 in 20 000 and 1 in 50 000. It is caused by mutations in the ABCD1 gene and is transmitted in an X-linked manner. Impaired activity of lignoceroyl-CoA ligase results in reduced beta-oxidation of saturated VLCFAs with their consequent accumulation. Depending on the phenotype this results in inflammatory CNS demyelination affecting the brain or cord, adrenal gland and testicular dysfunction, and peripheral neuropathy.

There are three phenotypes: Cerebral ALD (child, adolescent, or adult onset), adrenomyeloneuropathy (AMN) and primary adrenal failure. Onset of AMN is usually in young adults, with slowly progressive spastic paraparesis and sphincter dysfunction, mild peripheral neuropathy, and subtle cognitive change. Up to 50% of female heterozygotes manifest a mild neurological syndrome resembling AMN. Diagnosis is made by genetic testing of *ABCD1* mutations and detection of elevated serum VLCFA levels. Adrenal insufficiency is very common.

Treatment

Adrenal insufficiency should be treated with corticosteroid replacement. Early allogeneic haematopoietic cell transplantation (HSCT) can arrest the progression of, or even reverse, cerebral demyelination and is the treatment of choice for individuals with early stages of cerebral involvement in ALD. Autologous HSCT following genetic transduction (gene therapy) is considered if allogeneic options are limited. The mixture of oleic and eruric acid, known as Lorenzo's oil (LO), reduces the synthesis of VLCFAs by competitive inhibition of the enzyme responsible for the elongation of saturated fatty acids. It normalizes plasma levels of VLCFA, but results of clinical studies are conflicting and insufficient to recommend its use. HSCT should be offered early if neurological symptoms or MRI abnormalities develop. LO can be used for asymptomatic ALD, AMN, and Addison's only phenotypes.[11]

Refsum's disease

Refsum's disease is a rare autosomal recessive (AR) peroxisomal disorder, in which abnormal fatty acid metabolism results in pathological accumulation of phytanic acid, a branched-chain fatty acid, in tissues, including myelin sheaths and internal organs. The onset of symptoms is usually during childhood or adolescence. Neurological manifestations include peripheral neuropathy, retinitis pigmentosa, cerebellar ataxia, sensorineuronal hearing loss, and anosmia. Clinical diagnosis is confirmed by elevated serum phytanic acid levels.

Treatment

Management involves dietary restriction of phytanic acid. When this is not sufficient, intermittent plasmapheresis targeting LDL- and very-low-density lipoprotein (VLDL)-bound phytanic acid results in long-term improvement or stabilization. Stem cell therapy is under investigation in animal models.

Wilson's disease

This is an AR-inherited condition in which mutations in the hepatic ATPase ATP7B result in reduced excretion of copper into bile and consequent gradual accumulation of copper in the liver, brain, and cornea.

Clinical manifestations are predominantly hepatic (18–84% at presentation), neurological (18–73%), and psychiatric (10–100%). Neurological manifestations usually occur in the teens or 20s and typically include dysarthria, dystonia, tremor, and/or parkinsonism. A common presentation is deterioration in handwriting and loss of fine motor control which may then progress to tremor, rigidity, and dysphagia with drooling. Deposition of copper in the cornea produces the Kayser–Fleischer (KF) rings seen on careful slit-lamp examination in 98% of individuals with neurological features of Wilon's disease (WD).

Diagnosis requires LFTs, FBC, serum caeruloplasmin and copper levels, 24-h urinary copper excretion, and ocular slit-lamp examination to detect KF rings. Urinary copper excretion in response to a penicillamine (0.5 g) challenge and liver biopsy with copper quantification may be necessary. Genetic confirmation of ATP7B mutations in the patient and siblings is important.

Treatment

Asymptomatic patients

- Initial treatment (duration ranges from 6 months to 5 years):
  - trientine 750–1500 mg/day in two or three divided doses; or penicillamine 250–500 mg/day, increasing by 250 mg every 4–7 days to 1000–1500 mg/day in two divided doses;
  - zinc 50 mg tds if chelator not tolerated or declined.
- Adjunctive treatment: avoid copper-rich foods (shellfish, nuts, chocolate, mushrooms, organ meats), especially during year 1; pyridoxine 25–50 mg daily (penicillamine inactivates pyridoxine).
- Maintenance (lifelong):
  - zinc 50 mg tds or low dose (two-thirds of initial dose) of chelating agent.

Symptomatic patients

- Initial treatment (duration ranges from 6 months to 5 years):
  - penicillamine 250–500 mg/day, increasing by 250 mg every 4–7 days to 1000–1500 mg/day in two divided doses; or trientine 750–1500 mg/day in two or three divided doses (although unlicensed, ammonium tetrathiomolybdate should be considered in patients with

  prominent neurological involvement, in light of its lower incidence of initial neurological deterioration);
  - zinc 50 mg tds can be added to chelating agent in severe disease.
- Adjunctive treatment as described.
- Maintenance (lifelong):
  - zinc 50 mg tds or low (two-thirds) dose of chelating agent.

Acute liver failure or decompensated cirrhosis unresponsive to chelating agent

- Liver transplantation.

The initial treatment of WD should begin with a low dose of chelators and gradually reach a maintenance dose to prevent excessive copper release into the blood causing exacerbation of symptoms.[12]

Routine monitoring

WD patients receiving medication should be continuously monitored to assess treatment compliance, drug effectiveness, and adverse reactions. Serum copper and caeruloplasmin, LFTs, international normalized ratio (INR), FBC, and urinalysis should be measured at least 6-monthly and 24 h urinary copper excretion assessed annually. Estimated serum non-caeruloplasmin-bound copper should be measured if non-adherence or over-treatment is suspected.

Untreated, WD is universally fatal, with the development of progressive cirrhosis, severe dystonia, and akinetic mutism. Prognosis for patients who adhere to treatment is excellent, even in some who already have advanced liver disease. Life expectancy is normal in patients without advanced liver disease, but treatment must not be discontinued.

Copper chelators including D-penicillamine, trientine, and dimercaptosuccinic acid can significantly improve the liver injury and symptoms of WD patients but may have a limited effect on neurological symptoms. D-penicillamine was the first agent used. Its use is limited by side effects in up to a quarter of patients, including early sensitivity reactions and late nephrotoxicity, bone marrow toxicity, and dermatological disorders. Trientine hydrochloride has better tolerability and similar efficacy, and dimercaptosuccinic acid is used in China where trientine is not available. Chelators can cause permanent neurological deterioration in approximately 10% of patients during the initial phase of treatment. The mechanism of this paradoxical neurological deterioration may be explained by the release of large amounts of copper from the liver and other organs into the circulation, causing oxidative stress and damaging brain tissue. Ammonium tetrathiomolybdate is a powerful chelating agent recently advocated for use in WD, although as yet unlicensed. It may be particularly suitable for those with neurological involvement because of a lower (~4%) incidence of neurological deterioration after treatment initiation.

Zinc salts may be more appropriate for the treatment of asymptomatic patients or for the maintenance treatment of symptomatic patients. Zinc interferes with copper uptake from the gastrointestinal tract and promotes copper excretion through faeces by inducing metallothionein, an endogenous metal chelator. It is well tolerated and may have an increasing role in initial treatment in combination with penicillamine or trientine.

High-quality clinical trials for the drug treatment of WD are still lacking, therefore, individualized treatment options for patients are recommended. Individualized treatment can be determined based on the clinical features, efficacy and adverse effects of the drugs, and the experience of the physician. Liver transplantation is the only effective method to save patients with acute liver failure or with severe liver disease who fail drug treatment.

Symptomatic treatment of neurological manifestations

Beta-blockers can be used for tremor, or L-dopa, anticholinergics, benzodiazepines, or levetiracetam trialled for tremor phenotypically more akin to rubral tremor. Botulinum toxin can be helpful for head and facial tremor and focal dystonias. Treatment of generalized dystonia (see movement disorder chapter) may be indicated. Neuropsychiatric symptoms of depression, mania, and hypomania and psychosis should be managed with consideration of co-existent liver disease.

Evidence base

Large-scale randomized controlled trials are lacking to evaluate the efficacy of copper chelators and zinc. Guidelines for treatment include a 2008 consensus guideline from the American Association for the Study of Liver Diseases and a 2012 guideline from the European Association for the Study of the Liver. More recently, guidelines for the management of Wilson's disease from a neurological perspective were published.[13]

Porphyria

The porphyrias are a group of disorders of haem synthesis, resulting in the accumulation of porphyrin precursors aminolevulinic acid (ALA) and porphobilinogen (PBG) and of porphyrin intermediates uroporphyrin, coproporphyrin, and protoporphyrin. Clinical presentations of the AD-transmitted acute hepatic porphyrias (AHP) vary greatly and they can mimic many neurological or psychiatric conditions. There are four forms of AHP. The commonest is acute intermittent porphyria (AIP), caused by defects in the *HMBS* gene causing a lack of PBG deaminase. Variegate porphyria (VP) is caused by mutations in *PPOX* gene, hereditary coproporphyria (HCP) by mutations in *CPOX* gene and (ALADP) by defects in the *ALAD* gene.

Typically AHP presents with attacks of severe abdominal pain with autonomic dysfunction (tachycardia, orthostatic hypotension, labile BP, sweating, GI and urinary symptoms, fever) followed by neuropsychiatric disturbance with encephalopathy and subsequently subacute peripheral neuropathy (often beginning proximally). Red flags which should raise suspicion include abdominal pain, red urine, hyponatraemia, photodermatitis (in VP and HCP only) and encephalopathy with axonal neuropathy.

Attacks are precipitated by many commonly prescribed drugs (see websites of American Porphyria Foundation and European Porphyria Network for comprehensive and regularly updated lists), alcohol, reduced calorie intake, fluctuating sex hormones, stress, infection, smoking, and recreational drugs. Diagnosis is made acutely by measuring spot urine and 24-h urine for

PBG, ALA and porphyrins, and, if necessary, plasma and faecal porphyrins, and confirmed with genetic testing.

Treatment

Prompt diagnosis and treatment greatly improve prognosis and may prevent development of chronic neuropathic symptoms.[14]

Supportive measures

1. Eliminate precipitating factors.
2. Ensure optimal hydration and nutrition.
3. Treat symptoms with safe medications:

- pain: opiates (not pethidine);
- vomiting: ondansetron or prochlorperazine;
- agitation: chlorpromazine;
- hypertension/tachycardia: beta-blockers;
- seizures: clonazepam, diazepam, or magnesium sulphate.

Acute treatment of attacks

- *First line*: IV haematin 3–4 mg/kg for 4 days.
- *Second line*: carbohydrate loading (IV glucose 300–500 mg as 10% solution) only for attacks with mild pain and without severe manifestations.

Prophylaxis

- *First line*: avoid precipitating factors.
- *Second line*: givosiran, regular haematin (not approved).
- *Third line*: liver transplantation.

IV haematin therapy, available in Europe as Normosang® (haemarginate) or in the USA as Panhematin® (lyophilized haematin), inhibits hepatic ALA synthetase and produces significantly improved outcomes when given early (within 24 h of admission) in acute, severe attacks. Most attacks of acute porphyria should be treated promptly with IV haematin, certainly acute attacks associated with severe or prolonged pain, persistent vomiting, hyponatraemia, convulsions, psychosis, or neuropathy. Carbohydrate loading is only appropriate for mild attacks or until haematin becomes available, and haematin therapy should not be delayed because of ongoing carbohydrate loading.

The small proportion of AIP sufferers who develop recurrent attacks may benefit from prophylactic, regular haematin infusions, givosiran, or liver transplantation. Givosiran is a small interfering RNA that neutralizes excess ALAS1 mRNA in the liver and was approved in 2019.[15]

Phenylketonuria

Phenylketonuria is the most common inherited disorder of amino acid metabolism. Its inheritance is AR, and nearly all cases are due to the absence or mutation of the gene encoding hepatic phenylalanine hydroxylase (PAH), needed for the metabolism of phenylalanine into tyrosine. Large-scale screening programmes allow for diagnosis at birth. Another cause of hyperphenylalaninaemia (HPA) is tetrahydrobiopterin (BH4) deficiency.

BH4 is a molecular chaperone for PAH, and its loss results in an impaired ability to convert phenylalanine to tyrosine. Untreated, HPA results in progressive psychomotor decline in the first decade of life. The predominant feature is intellectual disability, with impairment of IQ ranging from severe to moderate. Other neurological features include epilepsy and abnormalities of gait, sitting posture, and stance. Early intervention with dietary phenylalanine restriction effectively prevents neurocognitive consequences.

Treatment

- *First line*: a low phenylalanine amino acid diet.
- *Second line*: sapropterin dihydrochloride.
- Elevated phenylalanine levels resistant to above: pegvaliase ERT.

A low phenylalanine amino acid diet is the mainstay of management and prevents progressive psychomotor decline. Sapropterin dihydrochloride is a synthetic analogue of BH4.[16] Recently ERT with pegvaliase was approved for patients with persistently elevated phenylalanine levels despite dietary restriction and sapropterin.[17]

Vitamin and nutrient deficiency syndromes

Vitamin deficiencies may occur as a result of inborn errors of metabolism, limited dietary intake, drugs/toxins or failure of absorption. Several vitamin and micronutrient deficiencies have specific neurological manifestations (see Table 19.3). Malabsorption syndromes may cause multiple deficiencies, with resultant neurological dysfunction. Treatment of neurological deficiency syndromes is with replacement, which prevents progression, and may or may not reverse established manifestations.

Table 19.3 Neurological deficiency syndromes

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Vitamin A	Night blindness, retinopathy, xerophthalmia, corneal ulceration, impaired immune function	Required for synthesis of retinal rhodopsin. Abundant in liver. Deficiency in fat malabsorption syndromes and malnourished	RDA 3000 iu (= 900 micrograms retinol) male, 2300 iu (= 700 micrograms retinol) female. Doses several fold higher than RDA recommended for fat malabsorption syndromes	Ataxia, alopecia, hyperlipidaemia, IIH bone, and muscle pain, hepatotoxicity, teratogenicity
Vitamin B1 (thiamine)	Wernicke's encephalopathy (WE)—acute encephalopathy with ophthalmoplegia and ataxia Korsakoff's syndrome—chronic amnestic syndrome following WE Adult beriberi—distal axonal S-M neuropathy (dry) ± cardiomyopathy (wet)	Beriberi seen where there is high reliance on white rice, following weight loss surgery Chronic alcoholism reduces absorption	RDA 1.2 mg male, 1.1 mg female (1.4 mg in pregnancy) WE—immediate 500 mg IV thiamine over 30 min tds for 2 days, then od for 5 days, then 100 mg po od Beriberi—50–100 mg IM or IV daily for 7–14 days	None. Excess is excreted in urine

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Vitamin B3 (niacin, nicotinic acid)	Pellagra—'dementia, dermatitis, diarrhoea'. Hyperpigmented rash on sun-exposed areas, red tongue, anxiety, insomnia, disorientation, delusions, encephalopathy	Seen when there is over-reliance on dietary corn, in chronic alcoholics, after weight loss surgery, in anorexia nervosa. Also seen in carcinoid syndrome, prolonged isoniazid therapy, Hartnup disease	RDA 16 mg (= 16 NE) male, 14 mg (= 14 NE) female Used as lipid-lowering agent at high doses (1–3 g daily)	Flushing High doses—nausea, vomiting, pruritus, constipation, elevated aminotransferases, myopathy, gout
Vitamin B5 (pantothenic acid, coenzyme A)	Paraesthesiae/dysaesthesia of feet, 'burning feet syndrome'	Very rare outside famine	RDA 5 mg	None. Excess is renally excreted
Vitamin B6 (pyridoxine)	Painful sensorimotor peripheral neuropathy, somnolence, confusion, glossitis, seborrhoeic dermatitis	Overt deficiencies rare. Deficiency usually due to drugs (isoniazid, hydralazine, penicillamine) or renal dialysis	RDA 1.3 mg (1.7 mg in >50 years, 1.9 mg in pregnancy)	Ataxic peripheral neuropathy described with chronic intake of 100 mg+ per day

(Continued)

Table 19.3 (*Contd.*)

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Vitamin B12 (hydroxocobalamin)		Pernicious anaemia, gastric and terminal ileum disorders, pancreatic insufficiency. Rare functional B12 deficiency due to abnormalities of transcobalamin proteins—high levels of precursors methylmalonic acid and homocysteine. Drugs blocking absorption include proton pump inhibitors, metformin, nitrous oxide anaesthesia18. Vegan diet	RDA 6–9 micrograms Deficiency treated with IM vitamin B_{12} 1 mg daily for 1 week, then 1 mg weekly for 4 weeks, then 1 mg 1- to 3-monthly if underlying disorder persists	None. Excess excreted in urine
			RDA 15–20 micrograms (600–800 iu) colecalciferol (vitamin D_3) Dose depends on nature and severity of deficiency	

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Vitamin D (calciferol)	Proximal myopathy Deficiency is associated with increased MS risk and worse disease course	Seen in hypoparathyroidism, chronic kidney disease, dietary deficiency, or inadequate exposure to sunlight	Severe deficiency (serum 25-hydroxyvitamin D levels <20 ng/mL or 50 nmol/L)–50 000 iu once weekly or 20 000 iu once to twice weekly for 6–8 weeks, then maintenance 1000–2000 iu daily	Hypercalcaemia/-uria, polydipsia/-uria, confusion, anorexia, vomiting, bone demineralization Upper limit 4000 iu daily
			Malabsorption/gastrectomy may require 10 000–50 000 iu daily, hydroxylated vitamin D metabolites (more readily absorbed), or sunlamp exposure	
			Insufficiency (20–30 ng/mL or 50–75 nmol/L)—1000–2000 iu daily probably sufficient	
Vitamin E (alpha-tocopherol)	Progressive ataxia, areflexia, and distal axonal neuropathy, neuromuscular disorders, haemolysis	Deficiency in fat malabsorption syndromes (abetalipoproteinaemia, cystic fibrosis, coeliac disease, cholestasis)	RDA 15 mg (= 22 iu natural or 33 iu synthetic vitamin E). Fat malabsorption syndromes—25–50 mg od	? increased risk of bleeding

(Continued)

Table 19.3 *(Contd.)*

	Deficiency syndrome	Key features	Recommended dietary allowance (RDA) and replacement	Toxicity
Copper	Myelopathy mimicking B_{12} deficiency, SACD, peripheral neuropathy, bilateral optic neuropathy, usually with anaemia and leucopoenia	After gastric surgery, prolonged total parenteral nutrition, excess zinc ingestion (competes for copper absorption in jejunum), enteropathies with malabsorption	RDA 900 micrograms. Deficiency—elemental copper 2 mg daily. Higher doses (8 mg daily, reducing by 2 mg every week to 2 mg) or IV doses may be required for severe symptoms initially. Zinc discontinued if relevant	Gastrointestinal symptoms, cardiac and renal failure, hepatic necrosis, encephalopathy Upper limit 10 mg daily
Selenium	Proximal myopathy and painful myalgia, cardiomyopathy	Rare. Linked with regional low soil selenium levels (e.g. in China)	RDA 55 micrograms	Gastrointestinal symptoms, hair and nail loss, encephalopathy, peripheral neuropathy Upper limit 400 micrograms daily
Strachan's syndrome	Painful polyneuropathy, sensory ataxia, optic neuropathy, hearing loss, mucocutaneous lesions	Initially described in malnourished in Jamaica and in prisoners of war (Jamaican neuritis, Cuban epidemic neuropathy). Due to multivitamin deficiency, particularly B vitamins	Early treatment with vitamin B and multivitamin preparations may resolve neuropathy > optic neuropathy	n/a

Neurological toxicity syndromes

The nervous system is susceptible to damage from a wide variety of environmental agents. Exposure may be deliberate or accidental and can occur via ingestion, inhalation, or absorption through the skin or mucous membranes. Table 19.4 includes the more commonly encountered neurotoxins, their typical neurological syndromes, and available treatment options.

Table 19.4 Treatable neurological toxicity syndromes

	Toxicity syndrome	Key features	Treatment
Alcohol	Acute intoxication and withdrawal, seizures, WE, Korsakoff's syndrome (thiamine deficiency), central and extrapontine myelinolysis, Marchiafava–Bignami disease, hepatic encephalopathy Chronic complications—cognitive impairment, cerebellar atrophy, seizures, peripheral neuropathy	No single cause of alcohol-related brain damage—as well as Korsakoff's syndrome, repeated episodes of intoxication and withdrawal, dietary neglect, vitamin deficiencies, traumatic brain injury, cerebrovascular event, and alcoholic liver disease may contribute	Abstinence, adequate nutrition Thiamine 100 mg od (see thiamine deficiency)
Lead	In adults, symmetrical pure motor polyneuropathy (upper > lower limbs), with prominent gastrointestinal disturbance. Blue line at gingival margin. Acute encephalopathy in children High CSF pressure, protein, and cells; basophilic stippling of marrow normoblasts. High blood lead levels, urine coproporphyrins	Commonest cause of heavy metal intoxication. Common sources include lead paint, water from lead pipes, burning or melting lead, and leaded gasoline	Eliminate exposure Chelation treatment with calcium EDTA, dimercaprol (British Anti-Lewisite—BAL) 3–5 mg/kg IM 4- to 6-hourly, or penicillamine 500 mg 6-hourly for 5 days Early treatment can improve neuropathy. Mannitol for raised ICP

(*Continued*)

Table 19.4 (*Contd.*)

	Toxicity syndrome	Key features	Treatment
Mercury	CNS toxicity—intention tremor, ataxia, sensory neuropathy, personality change, agitation, perioral paraesthesiae, progressive encephalopathy, visual field constriction, coma, and death Pneumonitis, inflamed gums, hypersalivation. Nephrotoxicity. Confirmed by high mercury levels in blood (>100 micrograms/L—normal <5 micrograms/L) and urine	Exists in metallic, inorganic, and organic forms (methylmercury in contaminated fish). Used in production of thermometers, mirrors, and latex paints, gold mining, and present in amalgam fillings (the latter not associated with toxicity). Metallic and organic forms are toxic to CNS; inorganic forms may be nephrotoxic. Exposure can be via inhalation of vapour, ingestion, or cutaneous absorption	Eliminate/limit exposure For CNS toxicity, prompt chelation with penicillamine 500 mg 6-hourly for 5 days, DMSA (dimercaptosuccinic acid) 10 mg/kg 8-hourly for 5 days, or dimercaprol (BAL) 3–5 mg/kg IM 4- to 6-hourly
Arsenic	Distal painful sensorimotor axonal neuropathy following acute poisoning or progressive with chronic exposure. Hyperpigmentation (dermatitis, jaundice) and autonomic involvement. Occasional encephalopathy. Mees' lines on nails in chronic exposure	Odourless, tasteless, highly toxic. Herbicides and pesticides, rodenticides, illicit alcohol, well water Blood, urine, hair, and nail arsenic levels	Acute poisoning—decontaminate skin, activated charcoal if recent ingestion (<1 h), and supportive careChelation with dimercaprol/BAL (3–5 mg/kg IM 4- to 6-hourly), DMSA, or unithiol (DMPS—2,3-dimercapto-1-propane sulfonate) until 24 h urinary arsenic <50 micrograms/L
Manganese	Progressive encephalopathy ('manganese madness') with fatigue, apathy, insomnia, hallucinations, and personality change Chronic exposure may lead to extrapyramidal features—parkinsonism with dystonia, neuropathy	Ubiquitous in living organisms and serves as an enzyme cofactor. Sources of toxicity include industrial exposure in iron and steel manufacturing and welding, and occasionally well water and total parenteral nutrition	Chelation with EDTA may help Levodopa

Table 19.4 (*Contd.*)

	Toxicity syndrome	Key features	Treatment
Methanol and ethylene glycol	Lethargy, progressive hypersomnolence, coma, seizures, visual loss (methanol), flank pain, and haematuria, renal toxicity (ethylene glycol), and profound metabolic acidosis	Present in antifreeze and de-icing solutions, windshield wiper fluid, solvents. Ingestion can occur deliberately when used as ethanol substitute, accidentally, by consumption of illicitly distilled alcohol (moonshine), deliberate self-harm	Block alcohol dehydrogenase with fomepizole 15 mg/kg IV, then 10 mg/kg 12-hourly. Ethanol used if fomepizole not available. Haemodialysis, IV sodium bicarbonate
Organophosphates	Acute cholinergic toxicity—salivation, lacrimation, mydriasis, bronchospasm, diarrhoea, urination, fasciculation, muscle weakness, central respiratory depression, coma, seizures Intermediate neurological syndrome in 40% after 1–3 days—diffuse muscle weakness (limb, bulbar, respiratory muscles), areflexia, cranial neuropathies Delayed neurotoxicity—painful distal paraesthesiae, followed by distal motor neuropathy	Used in pesticides and exposure common in agricultural settings. Inhibit acetylcholinesterase	Supportive care, ventilation, 100% oxygen Cholinergic symptoms—atropine 2–5 mg IV bolus, repeated as necessary Pralidoxime 30 mg/kg IV bolus over 30 min for cholinergic symptoms and neuromuscular dysfunction Benzodiazepines for seizures
Carbon monoxide	Constitutional symptoms, headache, dizziness, alterations in mental state ranging from mild confusion to coma and seizures Elevated serum carboxyhaemoglobin level Late neurocognitive deficits in up to 40%—cognitive and personality change, parkinsonism, other focal deficits	Clear, colourless, odourless gas. Poisoning from inadvertent or deliberate smoke inhalation, heating system dysfunction, poorly ventilated fuel burning devices, motor exhaust	Immediate 100% oxygen via non-rebreathing face mask Consider hyperbaric oxygen for severe intoxication

(*Continued*)

Table 19.4 (*Contd.*)

	Toxicity syndrome	Key features	Treatment
Cyanide	Acute poisoning—headache, confusion progressing to seizures and coma Cardiovascular dysfunction, cherry red flushing Delayed-onset parkinsonism Chronic exposure—tobacco–alcohol amblyopia, tropical ataxic neuropathy (TAN) Konzo (acute non-progressive spastic paraparesis)	Fire, industrial exposure (plastics and rubber production, pesticides, fertilizer, metallurgy) Konzo and TAN—reliance on underprocessed cassava during famine Cassava contains high levels of cyanogens and few sulphur-containing amino acids	Hydroxycobalamin 5 g IV stat If not available, use 'Cyanide Antidote Kit' (only after carbon monoxide poisoning excluded)—25% sodium thiosulfate 1.65 mL/kg IV plus amyl nitrite inhaled for 30 min every minute plus sodium nitrite 10 mg/kg IV

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Chapter 20

Uro-neurology

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Introduction

Urinary and sexual dysfunction associated with neurological disease have a tremendous impact on a patient's quality of life and are common in disorders such as multiple sclerosis (MS), extrapyramidal disorders, spinal cord injury, and dementia.

Two broad categories of neurogenic lower urinary tract dysfunction occur, depending to an extent on the site of the neurological lesion(s). These are termed storage dysfunction (detrusor overactivity/overactive bladder) and voiding dysfunction (detrusor sphincter dyssynergia or detrusor underactivity). These can occur individually or in combination and appreciation of this is essential for successful tailoring of therapies. For example, patients with MS not uncommonly have symptoms of urinary urgency, frequency, and urge incontinence from overactive bladder, together with voiding difficulties and incomplete bladder emptying due to detrusor sphincter dyssynergia. Treatment of detrusor overactivity in these circumstances can worsen incomplete bladder emptying.

This chapter outlines the management of urogenital dysfunction of neurological origin and specifically covers storage dysfunction (overactive bladder/detrusor instability), voiding dysfunction (detrusor sphincter dyssynergia or detrusor underactivity, also referred to as non-obstructive urinary retention), and erectile dysfunction.

Neurogenic lower urinary tract dysfunction

History taking and a bladder diary form the cornerstone of assessment of the patient with suspected neurological urinary dysfunction. Urine dipstick testing is important to rule out infection, and post-micturition bladder ultrasound to detect incomplete bladder emptying is often useful, as 50% of patients are unaware of incomplete voiding. Additionally, urodynamic testing can help to clarify the pattern of lower urinary tract dysfunction.

There are two main aims of management: 1) Improvement of symptoms and quality of life; and 2) Prevention of urological complications including recurrent urinary tract infections (UTIs), bladder stones, and renal impairment.[1]

Overactive bladder

The commonest type of neurogenic lower urinary tract dysfunction is overactive bladder (OAB, also referred to as detrusor overactivity or detrusor instability). Typical symptoms include urinary urgency and frequency, nocturia, and urge incontinence. Detrusor overactivity can also be demonstrated in urodynamic studies. OAB occurs as a result of lesions of the spinal cord or supra-pontine pathways. Typical causes include spinal cord injury, MS, cerebrovascular disease, dementia, and extrapyramidal disorders.

Treatment

All patients should be given advice to avoid exacerbating factors, i.e. to limit fluid intake to the recommended 1.5–2 L/day, to avoid caffeinated drinks and alcohol, and to undertake pelvic floor muscle training exercises. In addition to these, therapies used to treat the underlying disease may help to address urinary symptoms. Exclusion of chronic urinary tract infection prior to treatment is important.

Pharmacological

- *First line*: antimuscarinic medications (see Table 20.1); β3-adrenoceptor agonists alone or combined with antimuscarinic.
- *Second line*: desmopressin.
- *Third line*: intravesicular botulinum toxin.

Neuromodulation

1. Percutaneous or transcutaneous tibial nerve stimulation (PTNS/TTNS).
2. Sacral neuromodulation.

Surgical in select patients

1. Augmentation cystoplasty.
2. Urinary diversion.

Evidence base

1. *Antimuscarinic agents*: these are very effective drugs, typically used first-line for OAB symptoms. Meta-analyses have demonstrated there are no major differences in efficacy between the different agents, and they share a similar side effect profile.[2] This includes central effects such as dry mouth and cognitive impairment. Individual variations relate to their muscarinic receptor selectivity, pharmacokinetics, and metabolism (see Table 20.1). Importantly, antimuscarinics may worsen the efficiency of bladder emptying so should be used with caution in those with mixed OAB and incomplete bladder emptying.

Table 20.1 Antimuscarinic medications

Generic	Dose (mg)	Frequency	Receptor subtype	Elimination half-life (h)
Tolterodine	2 (4)	bd (od)	Non-selective	2.4(8.4)
Trospium	20	bd	Non-selective	20
Oxybutynin	2.5–5	bd to qdsod	Non-selective	2.3
Oxybutynin XL	5–30	bd to qdsod	Non-selective	13.2
Propiverine	15	od to qds	Non-selective	4.1
Darifenacin	7.5–15	od	Selective M3	3.1
Solifenacin	5–10	od	Selective M2 plus M3	40–68
Propantheline	15	tds	Non-selective	<2
Fesoterodine	4–8	od	Non-selective	7

bd, twice daily; od, once daily; qds, four times daily.

2. *Desmopressin*: a synthetic form of the antidiuretic hormone (ADH) vasopressin, which works by temporarily reducing urine production by promoting reabsorption of water by the renal collecting ducts. It can be effective for troublesome nocturia associated with OAB not responsive to antimuscarinics, but its use is limited by side effects of hyponatraemia, fluid retention, and seizures.[3] One randomized control trial (RCT) demonstrated that 34% of patients with OAB experienced halving of the number of nocturia episodes with desmopressin, compared to 3% with placebo.[4]

3. *β3-adrenergic receptor agonists:* These agents induce direct relaxation of the detrusor smooth muscle. Two phase 2 and five phase 3 RCTs showed that mirabegron, the first in class of these agents, is efficacious and appears to be well tolerated in the treatment of OAB[5] (see drug monograph Mirabegron, p p. 529–31). Vibegron, which has more selective activity on β3 receptors, has recently been licensed in USA.

4. *BTX-A*: cystoscopy-guided botulinum toxin injections into the detrusor muscle significantly improves urinary urgency, incontinence, bladder capacity, and detrusor pressures in patients with OAB. The beneficial effect of each procedure lasts for ~8–11 months. Up to 40% of patients need to perform intermittent self-catheterization (ISC), following botulinum toxin injection (compared to 10% at baseline); hence, patients should be made aware of this prior to treatment. In one RCT, onabotulinum toxin A reduced mean incontinence by 23 episodes per week, compared to nine episodes per week in the placebo group ($p < 0.001$). Quality of life scores were also significantly improved.[6] No comparator studies exist between onabotulinumtoxinA and abobotulinumtoxinA though outcomes appear similar in animal models.

Neuromodulation

This most commonly involves PTNS, TTNS, or sacral neuromodulation. The mechanism by which these techniques work is unknown. PTNS and TTNS are minimally invasive techniques involving electrical stimulation of the posterior tibial nerve with a fine-gauge needle/transdermal electrode respectively.

Sacral neuromodulation is a two-stage surgical procedure whereby the S3 nerve root is electrically stimulated. It has been shown to be beneficial in treating detrusor overactivity/urge incontinence, as well as non-obstructive urinary retention.

Evidence base

In a double-blind, randomized-controlled study comparing 12 weeks of PTNS to a sham treatment, 55% of patients had response to treatment, compared to 21% of the control group ($p < 0.001$).[7]

Sacral neuromodulation has been studied in a small number of neurological patients and has shown benefit in patients with MS. In patients with early spinal cord injury, it can reduce bladder pressures and prevent the development of detrusor overactivity, when compared to controls.[8]

Voiding dysfunction/Non-obstructive urinary retention

Voiding dysfunction may occur in the context of neurological disease affecting the spinal or infraspinal pathways. When it occurs in the context of spinal cord disease, it is usually due to incoordination of detrusor and sphincter contraction and relaxation (detrusor sphincter dyssynergia). Conversely, incomplete bladder emptying arising from lesions of infraspinal pathways is usually because of poorly sustained detrusor contractions (detrusor underactivity) ± non-relaxation of the sphincters. Causes include lesions of the conus medullaris, cauda equina, lumbosacral roots, and less commonly peripheral nerves. Spina bifida and MS commonly cause a mixture of storage and voiding dysfunction. Potential complications of voiding dysfunction with incomplete bladder emptying include recurrent UTIs and less commonly renal failure due to reflux.

Treatment

Compared to OAB, there are fewer management options for patients with urinary retention.

- *First line*: catheterization is the mainstay of management. Intermittent clean self-catheterization is preferable to an indwelling urethral or suprapubic (preferable) long-term catheter in the first instance.
- Alpha1-adrenergic blockers are occasionally considered.
- *Second line*: sacral neuromodulation is useful in some patients with chronic voiding dysfunction, especially with a primary disorder of urethral sphincter relaxation (Fowler's syndrome).

Evidence base

Catheterization has been demonstrated to reduce deterioration of kidney function in patients with urinary retention after spinal cord injury. However, potential side effects include urinary tract infection and trauma. Clean intermittent self-catheterization (CISC) is preferred over indwelling catherization (grade A recommendation) despite a low level of evidence.

Regarding sacral neuromodulation, one systematic review of 14 studies (one RCT and 13 observational studies), the mean difference in post-void residual decreased by 236 mL ($p < 0.0001$), and voided volume increased by 299 mL ($p < 0.0001$), suggesting that this is a highly effective treatment.[9,10] However, there is a high complication rate, with 53% needing surgical revision of their implant at some point.

Disorders of sexual function

Normal sexual function involves complex neurovascular processes. Only erectile dysfunction is currently amenable to pharmacological intervention.

Erectile dysfunction

Neurological conditions, such as traumatic brain injury, stroke, spinal cord injury, MS, PD, MSA, and epilepsy, can predispose an individual to erectile dysfunction. However, it is often multifactorial, and common causes or aggravating factors must be addressed. These include psychological factors depression and anxiety, iatrogenic causes (for example antidepressants, β-blockers), comorbidities (diabetes, peripheral vascular disease).

Treatment

Factors that influence sexual function in patients should be addressed individually. Psychological therapies and pelvic floor exercises may be of benefit to some individuals.

- *First line*: phosphodiesterase 5 (PDE5) inhibitors are effective in treating erectile dysfunction of neurological origin. There are various formulations with variable potency and duration, including sildenafil, tadalafil, and vardenafil.
- *Second line*: vacuum constriction devices.
- *Third line*: intraurethral prostaglandin E1 or phentolamine gels; intracavernous injections of prostaglandin E1, papaverine, or phentolamine.
- *Fourth line*: implants.

Evidence base

The three PDE5 inhibitors sildenafil, tadalafil, and vardenafil have statistically similar efficacy and safety profiles.[11] The commonest side effects are headache and flushing. One RCT of sildenafil for erectile dysfunction in patients with MS demonstrated significantly increased erectile function scores, compared to placebo ($p < 0.001$).[12] Vacuum constriction devices can improve erections and sexual intercourse in up to 80% of patients in one retrospective study[13]; however, trials have demonstrated a dropout rate of around 30%, due to complaints of bruising, pain, and numbness of the penis. Intracavernous injections have a similar efficacy rate in patients[14] but have a higher dropout rate, due to the continued use of needles which lends itself to complications.

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Chapter 21

Drugs causing neurological disease

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Introduction

Listed in this chapter are medications known to cause or aggravate neurological disease. Drugs that can cause and/or exacerbate parkinsonism and MG are listed in their respective chapters; please see Chapter 12, Parkinson's disease and parkinsonism, and Chapter 11, Disorders of the neuromuscular junction, respectively. Given its similarity to Parkinson's hyperpyrexia syndrome, neuroleptic malignant syndrome is included in Chapter 12.

Cerebellar syndrome

The development of a cerebellar syndrome has been reported as a side effect of many drugs. For the majority of medications, reversible ataxia typically occurs within days to weeks of starting a new medication or increasing the dose of a previously established medication. Individuals who have pre-existing ataxia, are taking multiple medications, or who are elderly or very young are more at risk of these side effects. A list of medications recognized to have this adverse effect is included below.

A few medications have also been reported to result in progressive cerebellar ataxia with concomitant cerebellar atrophy occurring several years after medication initiation (see Table 21.1). This may not be reversible on stopping the medication. The most commonly cited causes for this are lithium, phenytoin, and valproate.

Table 21.1 Drugs reported to causing a cerebellar syndrome

Aminoglycosides (e.g., gentamicin)
Amiodarone
Atorvastatin
Barbiturates (e.g. phenobarbital)
Capecitabine
Carbamazepine
Chlordiazepoxide
Ciprofloxacin
Clobazam
Clomipramine
Clonazepam
Colistin
Cyclosporin
Cytarabine
Dextromethorphan
Docetaxel
Flunitrazepam
Fluorouracil
Gabapentin
Interferon
Irinotecan

Table 21.1 (*Contd.*)

Lamotrigine
Levamisole
Lidocaine
Lithium
Maprotiline
Metronidazole
Mexiletine
Mitotane
Nitrazepam
Octreotide
Oxcarbazepine
Paclitaxel
Phenytoin
Piperazine
Pregabalin
Propafenone
Propofol
Raltegravir
Retigabine
Tacrolimus
Thiopental
Tiagabine
Topiramate
Tramadol
Tretinoin
Triazolam
Valproate
Vigabatrin
Zonisamide

Chorea/Tardive dyskinesia

Tardive dyskinesias occur whilst taking a medication or within a few weeks of stopping a medication (withdrawal-emergent dyskinesia). Individuals are typically exposed to medication for over 3 months, although tardive dyskinesias may emerge after only a month in the elderly. The most commonly implicated drugs are those with anti-dopaminergic activity e.g. antipsychotics. Several of the medications included in Table 21.2 have a degree of activity on dopamine receptors even though this is not considered to be their primary therapeutic mechanism of action.

Table 21.2 Drugs reported to cause chorea/tardive dyskinesia

Anti-inflammatories (sulfasalazine)
Antibiotics (ciprofloxacin, levofloxacin)
Antidepressants (amitriptyline, clomipramine, desipramine, imipramine, paroxetine, sertraline, venlafaxine)
Antiemetic drugs (cyclizine, metoclopramide)
Antihistamine (cyproheptadine)
Antihypertensive medications (alpha-methyldopa, reserpine)
Antiparkinsonian agents (amantadine, anticholinergics, dopamine agonists, levodopa)
Atypical antipsychotics (aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
Benzodiazepines and related drugs (clorazepate, diazepam, flunitrazepam, triazolam, zopiclone)
Calcium antagonists (cinnarizine, diltiazem, flunarizine, nifedipine, nimodipine, nitrendipine, verapamil)
Catecholamine-depleting agents (tetrabenazine)
CNS stimulants (amphetamine, cocaine, methylphenidate, pemoline)
Hormones (levothyroxine, oestrogens)
Other dopamine-receptor blockers (metoclopramide, sulpiride, tiapride)
Typical antipsychotics (chlorpromazine, chlorprothixene, droperidol, flupentixol, fluphenazine, haloperidol, trifluoperazine, promethazine, zuclopenthixol)
Others (aminophylline, baclofen, digoxin, ethanol, lithium, manganese, methadone, theophylline)

Pro-dopaminergic agents e.g. levodopa also commonly lead to choreiform movements ‘levodopa induced dyskinesia’ in susceptible individuals, i.e. those with nigrostriatal damage such as Parkinson’s disease. This is thought to reflect the effect of pulsatile exposure to levodopa on damaged nigrostriatal pathways rather than the medications per se, as it does not occur in conditions without nigrostriatal pathology e.g. restless legs syndrome.

Rarely individuals exposed to high levels of stimulants can develop an acute choreoathetosis, which typically resolves spontaneously, e.g. amphetamines/cocaine.

Management

Drug cessation/switch:

1. Where possible consider slowly reducing and discontinuing the culprit drug. Improvement may take weeks to months and overall rates of complete remission may be low. Patients may experience a transient

increase in symptoms during drug withdrawal (withdrawal-emergent dyskinesia).

2. If this is not possible then switching to a different type of medication may be effective (although there is little supporting evidence for this). Second-generation antipsychotics such as quetiapine and clozapine have lower D2 affinity and are less likely to cause tardive dyskinesia.

Treatment:

If drug withdrawal is not possible or ineffective then several medications including two newly licensed (in the USA currently, not UK) vesicular monoamine transporter 2 (VMAT2) inhibitors, can be trialled.

First line:VMAT2 inhibitors—(deutetrabenazine, tetrabenazine, or valbenazine)

Second line: Amantadine and clonazepam (short-term <3 months).

Other: botulinum toxin injections, ginkgo biloba

Evidence base

VMAT2 inhibitors

Both deutetrabenazine and valbenazine have RCT evidence demonstrating their utility in the treatment of tardive dyskinesia. The abnormal involuntary movement scale (AIMS) score changed by –1.9 and –3.2 with 40 and 80 mg of valbenazine respectively vs. –0.1 with placebo ($p < 0.002$), and –3.2 and –3.3,[1] with 24 and 36 mg of deutetrabenazine, respectively, when compared to –1.7 with placebo ($p < 0.04$).[2] There was no significant difference in psychiatric side effects between active and placebo groups but somnolence was more common in the active groups.

Tetrabenazine is an older drug. There are no RCTs investigating its use in the context of tardive dyskinesia. Small studies looking at high-dose tetrabenazine have shown an average improvement of >50% in the AIMS scores, although these doses were associated with a significant risk of drowsiness, parkinsonism, and depression.

Off-label pharmacological approaches

There are several small studies looking at the use of amantadine for the treatment of tardive dyskinesia. Small improvements in the AIMS score were demonstrated at doses of up to 400 mg/24 h.

Several small series have also reported on the use of botulinum toxin injections into peri-oral muscles for the treatment of focal tardive dyskinesia. Reported benefits were non-significant in a small trial n = 12.[3] Injections are likely to be more effective when there is a significant dystonic component.

CNS Demyelination

Drugs and toxins are rare causes of CNS demyelination. There are two main pathophysiological mechanisms:

1) Immune dysregulation causing a secondary demyelinating syndrome: this results in focal or multifocal neurological deficit/s associated with focal or multifocal demyelinating lesions on MRI.

Optic neuritis, transverse myelitis, ADEM, and relapsing-remitting multiple sclerosis are typical clinical manifestations.

2) Toxic leukoencephalopathy: the drug has a direct toxic effect on myelin, oligodendrocytes, and associated cells, resulting in an acute or chronic demyelinating syndrome typically characterized by encephalopathy and diffuse involvement of the white matter on MRI.

CNS demyelination secondary to immune dysregulation

The drugs most often implicated are listed in Table 21.3[4]:

Management

There are no evidence-based trials for treatment of these disorders. The offending agent should be removed, and the inflammatory disorder treated in a similar fashion to the primary syndrome depending on symptom severity, e.g. corticosteroids +/– plasma exchange (please see Chapter 6, Multiple sclerosis and related disorders). Patients should be monitored following recovery for relapse in case this represents the first presentation of a relapsing-remitting disorder, although repeated exposure to the causative drug should also be considered (e.g. continued cocaine use).

Toxic leukoencephalopathy

Several different medications can cause a toxic leukoencephalopathy. The time course can be acute, subacute, or chronic, depending on the dose, repeated exposure, and as yet unidentified individual patient risk factors. The disorder may be mild, manifesting with confusion and subtle personality changes, or severe with apathy, somnolence, and even akinetic mutism and coma. The MRI white matter changes tend to correlate with the severity of symptoms and reflect the underlying pathological changes of myelin-associated oedema, demyelination and, if severe, oligodendrocyte and axonal loss.

The main drugs implicated are listed in Table 21.4.[5,6]

Management:

Treatment is typically supportive. A good recovery can be anticipated if the insult is not severe enough to result in necrosis. The offending agent should be removed and avoided in the future. Corticosteroids and plasma exchange are occasionally used based on case series in patients with severe symptoms.

Table 21.3 Drugs reported to cause CNS demyelination

TNF alpha inhibitors, e.g. adalimumab, used in rheumatological disorders and inflammatory bowel disease.
Immune checkpoint inhibitors, e.g. ipilimumab and nivolumab, used as anti-cancer therapies.
Levamisole—an anthelminthic drug frequently used to cut cocaine.
Tyrosine kinase inhibitors, e.g. imatinib/nilotinib.
Bevacizumab—an anti-VEGF antibody.

Table 21.4 Drugs reported to cause a toxic leucoencephalopathy

Anti-microbials:	
o	Amphotericin B, metronidazole
Chemotherapy:	
o	Carmustine, cisplatin, cranial irradiation, methotrexate (intrathecal > intravenous)
Drugs of abuse:	
o	Cocaine, ethanol, heroin (inhaled or intravenous) and to a lesser extent other opioids etc,
Immunosuppressants:	
o	Ciclosporin, tacrolimus
Environmental toxins:	
o	Carbon monoxide, organic solvents

Dystonia

Dystonic reactions can be caused by several medications listed in Table 21.5. They can be either:

1) *Acute*: on first or limited exposure to a medication when it is termed an acute dystonic reaction, e.g. oculogyric crisis, pseudo macroglossia (tongue protrusion)
2) *Chronic*: After long-term exposure (typically months to years) when it is termed a tardive dystonia.

Table 21.5 Drugs reported to cause dystonic reactions

Antihistamines
Antiemetics (domperidone, metoclopramide, and prochlorperazine)
Antimalarials (e.g. chloroquine)
Anticonvulsants (carbamazepine, gabapentin, lamotrigine, phenytoin, phenobarbital)
Antipsychotics (amisulpride, aripiprazole, chlorpromazine, droperidol, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, ziprasidone)

Management

Acute dystonic reactions

These reactions are typically transient and reversible upon removing the offending drug. They can be distressing and occasionally life-threatening, for example, if they involve the larynx. Treatment with anticholinergics is often rapidly effective. The half-life of many antipsychotics is longer than that of the anticholinergics, hence patients should be placed on a small oral dose of the anticholinergic for a further 3–7 days to prevent recurrence of symptoms.

Treatment

- *First line*: Anticholinergics, e.g. benztropine 1–2 mg IV/PO stat, followed by 1–2 mg BD, diphenhydramine 50 mg IV/PO stat, followed by 25 mg BD; or procyclidine 5–10 mg PO/IV stat, followed by 2.5 mg PO TDS.
- *Second line*: Benzodiazepines, e.g. diazepam or lorazepam.

Tardive dystonia

Tardive dystonia typically occurs after prolonged use of the offending medication (most commonly antipsychotics). Where possible the medication should be stopped or switched to an agent less likely to cause these symptoms, e.g. clozapine. If this is not possible or drug modification has not been effective, then botulinum toxin and other typical anti-dystonic agents can be effective in this scenario and treatment is the same as for idiopathic dystonia (see Chapter 13, Hyperkinetic movement disorders). In severe cases not responding to first-line therapy, DBS can be effective.

Myoclonus

Drug-induced myoclonus is one of the most common causes of myoclonus. The exact incidence is not known but is likely under-reported in most studies. One small study of ~100 patients treated with tricyclic antidepressants found that 30% had myoclonus, although this was clinically significant in only ~10%.[7]

Drug-induced myoclonus can be focal, segmental, multifocal, or generalized. Some drug classes are more likely to present with certain distributions than others. It is typically reversible upon removing the offending drug. Myoclonus is more likely to occur when two or more drugs are used concurrently. The proposed mechanisms vary depending on the drug but are most commonly secondary to increased central serotonin levels and altered activation of GABAergic or glutamatergic pathways. In patients taking multiple serotonergic agents, myoclonus may manifest as part of a generalized serotonin syndrome.

Most agents present with either generalized or multifocal myoclonus. Rarely, focal myoclonus can occur, e.g. tricyclic antidepressants and amantadine are well recognized to cause an isolated jaw myoclonus, whilst antipsychotics may cause postural or action-induced myoclonus. Certain antibiotics such as the cephalosporins, particularly when given at either high IV doses or in the presence of renal impairment, can induce myoclonus in the context of encephalopathy, sometimes with seizures and nonconvulsive status. Drugs that are recognized to cause myoclonus are listed in Table 21.6.

Table 21.6 Drugs reported to cause myoclonus:

Amantadine
Antibiotics (e.g. penicillins, cephalosporins, penems, quinolones, isoniazid)
Anticonvulsants (e.g. gabapentin, pregabalin, lamotrigine, phenytoin, phenobarbital)
Antidepressants (e.g. lithium, SSRIs, TCAs)
Antidiarrheal agents (bismuth subsalicylate)
Benzodiazepines (and their withdrawal)
Calcium channel blockers
Contrast media
Dopamine antagonists, e.g. antipsychotics
Levodopa
Opioids (e.g. morphine)
Propofol

Myopathy

Myopathy is an uncommon but important side effect of several different drug classes (listed in Table 21.7). Clinical presentations and potential

Table 21.7 Drugs reported to cause myopathy

Aminocaproic acid
Amiodarone
Antimalarials—chloroquine, hydroxychloroquine
Colchicine
Emetine (in ipecac)
Etretinate
Glucocorticoids—especially 9-α-fluorinated (dexamethasone, betamethasone, triamcinolone)
Interferon-alpha
Lipid-lowering drugs—statins, fibrates, nicotinic acid, ezetimibe
Penicillamine (myositis)
Perhexiline
Recreational drugs—alcohol, cocaine
Streptokinase
Vincristine
Zidovudine

underlying pathological mechanisms vary with different medications. Several medications, e.g. corticosteroids and statins may cause a myopathy via multiple different pathological processes. Common presentations include an acute toxic myopathy, a chronic proximal myopathy, and rarely secondary inflammatory myopathies and focal myopathies. Drug related myopathy may be more common in patients with underlying neuromuscular disease, and sometimes a drug may unmask a previously undiagnosed hereditary muscular disorder.

Acute toxic myopathy

Acute toxic myopathy typically occurs within days to months of starting or increasing a new medication. There is a wide spectrum of presentation from asymptomatic elevated CK to severe cases with widespread muscle necrosis, subacute generalized weakness, and even rhabdomyolysis. Common culprits include statins, alcohol excess, cocaine, and heroin abuse.

Inflammatory myopathy/myositis

A small number of agents, e.g. D-penicillamine and interferon-α can trigger a secondary inflammatory myositis. Symptoms typically improve on removal of the causative agent but may need immunosuppressive therapy acutely. Statin therapy is also causally linked with anti-HMG CoA reductase myositis, an aggressive form of autoimmune necrotizing myositis. A minority of patients may improve with removal of the statin, but the majority will need potent and prolonged immunotherapy (see Disorders of muscle, Chapter 10).

Chronic proximal myopathy

Another form of myopathy can occur when medications cause dysfunction of intrinsic muscle metabolic pathways, leading to a subacute or chronic progressive myopathy. For instance, zidovudine inhibits mitochondrial mtDNA replication and lysosomal dysfunction can occur with antimalarial medications.

Corticosteroids can also cause a myopathy, the underlying mechanism for this is unclear. Chronic muscle atrophy is common with prolonged steroid use, particularly at high doses. This is usually generalized, although focal laryngeal weakness can occur with regular use of inhaled steroids. Corticosteroids may rarely contribute to a critical illness myopathy in acutely unwell patients taking high-dose steroids. The CK in steroid-induced myopathies is typically normal or mildly raised. The prognosis is good provided the steroids can be stopped, although recovery may take months.

Peripheral neuropathy

Several drugs can cause a peripheral neuropathy, and medication accounts for between 2–4% of cases of peripheral neuropathy.[8] The mechanism varies depending on the specific drug. There may be a direct toxic effect resulting in damage to the axon, myelin or neuron, or an indirect effect by generation of a secondary immune-mediated neuropathy.

Most commonly a medication causes an axonopathy or myelinopathy, resulting in pure sensory or combined sensorimotor features. The degree and speed of onset of neuropathy depend on the medication type, dose, and duration of exposure. Certain medications may preferentially affect large, myelinated fibres (e.g. platinum-containing compounds) or small fibres (e.g. vinca alkaloids). Neuropathy is a common complication of chemotherapeutic regimes and can limit treatment protocols.

A phenomenon referred to as 'coasting' is seen after discontinuation of certain chemotherapeutic agents, particularly platinum containing compounds, where the neuropathy may progress for 3–6 months before stabilizing. Management is focused on removal of the causative agent where possible and treatment of neuropathic pain if present.

Drug-induced neuronopathies are rare. A dorsal root ganglionopathy with or without axon/myelin involvement is the typical presentation, resulting in progressive sensory loss and prominent sensory ataxia.

Drug-induced immune-mediated neuropathies such as GBS, CIDP, MFS, or vasculitis are increasingly recognized due to the escalating use of immunomodulatory and immunosuppressant agents in inflammatory and neoplastic conditions. In these cases, drug withdrawal is not always sufficient and short or long-term immunosuppressant therapy may be required.

Alcohol and environmental toxins such as heavy metals (arsenic, thallium, lead, gold and mercury) can also cause peripheral neuropathy, typically after chronic exposure.

A summary of drugs recognized to cause peripheral neuropathy, and the proposed underlying mechanism are listed in Table 21.8.

Table 21.8 Drugs reported to cause peripheral neuropathy

Amiodarone (M)
Antibacterials—metronidazole (A) isoniazid (A) nitrofurantoin (N), ethambutol (A)
Antineoplastic agents—vinca alkaloids (A), taxanes (paclitaxel, docetaxel) (A)
Antirheumatics—chloroquine (M—plus myopathy)
Anti-TNFα therapies, e.g. infliximab (IM)
Bortezomib (A)
Disulfiram (A)
HAART—zalcitabine, didanosine, stavudine.
Immune checkpoint inhibitors, e.g. pembrolizumab (IM)
Levodopa (A)
Nitrous oxide (A—plus myelopathy)
Nucleoside reverse transcriptase inhibitors, e.g. zidovudine (A)
Phenytoin (A)
Platinum compounds (N)
Pyridoxine (N)
Mechanism (A—axonal, M—myelin, N—neuronopathy, IM—immune-mediated)

Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

PRES and RCVS are two similar but clinically distinct syndromes described in more detail below. Recognized triggers for both of these conditions overlap considerably and include hypertension (including pre-eclampsia and eclampsia), autoimmune disorders, sepsis, and certain medications. The two main groups of medications implicated are anti-cancer and immunosuppressive agents, and those that can trigger accelerated hypertension. Drugs recognised to trigger PRES and/or RCVS are listed in Table 21.9.

PRES

PRES is characterized by a variety of neurological symptoms and classical neuro-imaging findings. Common symptoms include encephalopathy, seizures, headache, and focal neurological deficits (typically visual). Most patients have hypertension or an acute increase in blood pressure. Radiological evaluation demonstrates vasogenic oedema, typically posterior involving the occipital and posterior parietal regions, although the anterior lobes may rarely be affected. The underlying pathology is unclear, but is thought to reflect endothelial dysfunction, with failure of vascular autoregulation and an abnormal vasoconstriction response resulting in vasogenic oedema.

RCVS

RCVS is an overlapping clinical entity characterized by recurrent thunderclap headaches, and potentially focal neurological deficit related to ischaemic stroke and haemorrhage. Multifocal vasoconstriction of the CNS vascular tree is seen radiologically. The underlying pathology is thought to be related to impairment of CNS vascular autoregulation and secondary segmental vasoconstriction.

Table 21.9 Drugs reported to cause PRES and RCVS

Anti-angiogenic agents (e.g. bevacizumab)
Alcohol withdrawal
Antiretrovirals (e.g. indinavir)
Chemotherapy (e.g. cisplatin, gemcitabine, methotrexate, vincristine, fludarabine, cytarabine, bortezomib, sorafenib, sunitinib)
Cocaine
Corticosteroids
Immunosuppressive agents (e.g. tacrolimus, ciclosporin)
Interferon-alpha
IV immunoglobulin
Monoclonal antibodies (e.g. rituximab, infliximab, alemtuzumab)

There is considerable overlap between the two conditions. RCVS has been associated with vasogenic oedema similar to that seen in PRES, and conversely, vasoconstriction similar to that occurring in RCVS has been described in PRES. Precipitating factors, including drugs are similar for both PRES and RVCS (see list earlier).

Management

The treatment includes removal of potential causative agents and rapid correction of hypertension. Anticonvulsants are commonly required in the short term to prevent further seizures, although, in the absence of permanent cortical injury, epilepsy as a long-term consequence of PRES or RCVS is rare.

Seizures

Seizures are a potential complication of the toxic or withdrawal effects of several different prescribed medications (listed in Table 21.10). Medications either promote excitatory biochemical influences or reduce inhibitory

Table 21.10 Drugs reported to cause seizures

AChEIs (e.g. donepezil, memantine, rivastigmine)
Antibacterials (e.g. cephalosporins, quinolones, fluoroquinolone)
Anticholinergics (e.g. tolterodine, oxybutynin, trihexyphenidyl)
Anticonvulsants (withdrawal)
Antidepressants (e.g. amitriptyline, bupropion, venlafaxine)
Antifungals (e.g. amphotericin B)
Antihistamines (e.g. diphenhydramine)
Antimalarials
Antiretrovirals (e.g. efavirenz, zidovudine)
Antivirals (e.g. aciclovir, ganciclovir)
Baclofen (withdrawal)
Benzodiazepines (withdrawal)
Bronchodilators (e.g. aminophylline, theophylline)
Chemotherapy (e.g. busulfan, cisplatin, methotrexate, vincristine)
Immunomodulators (e.g. ciclosporin, mycophenolate, prednisolone, tacrolimus)
Isoniazid
Lithium
Methylphenidate
Opioids (e.g. tramadol)
Recreational (alcohol, cocaine, amphetamines, MDMA) Environmental toxins (organophosphates)

influences on neurons, resulting in seizures. There are also several medications that interact with anti-seizure medications potentially increasing their metabolism and reducing their efficacy, resulting, indirectly in seizure generation (for further information see the individual drug monograph interactions section). In severe cases this can lead to status epilepticus.

The main management strategies are withdrawal of the offending agent (or replacement if the seizure has resulted from drug withdrawal) and obtaining rapid seizure control. If status epilepticus results, then the standard management algorithm should apply (see Chapter 3, Epilepsy).

Serotonin syndrome

Serotonin syndrome is a potentially fatal condition that results from excess serotonergic activity. It may occur either through overdose of serotonergic drugs, administration of two or more drugs with serotonergic activity or co-administration of a drug which acts to elevate plasma levels of serotonergic drugs or serotonin directly. Onset of symptoms and signs typically occurs within 24 h
of changes in medication.

The most implicated medications are SSRIs. Other potentially responsible medications are listed in Table 21.11:

Serotonin syndrome is characterized clinically by three groups of symptoms:

1. Changes in mental status i.e. agitation and confusion.
2. Autonomic hyperactivity i.e. diaphoresis, diarrhoea, dilated pupils, and hyperthermia, as well as changes in heart rate and blood pressure.
3. Neuromuscular abnormalities, i.e. clonus, tremor, hyperreflexia, and muscle rigidity.

Management

1. Stop offending medication(s).
2. Supportive management: Aim to correct abnormal vital signs (e.g. with intravenous fluids and cooling).
3. Benzodiazepines, e.g. diazepam or lorazepam for myoclonus and agitation.

Table 21.11 Drugs reported to cause serotonin syndrome

Antibiotics: e.g. linezolid
Antidepressants: NDRIs, e.g. buspirone, SSRIs, SNRIs, and TCAs
Antiemetics: 5-HT3 receptor antagonists e.g. ondansetron
Antipsychotics: e.g. risperidone, olanzapine
Drugs of abuse: e.g. amphetamines, cocaine, heroin, LSD, MDMA
MAOIs: e.g. rasagiline, selegiline
Opioids: e.g. methadone, tramadol
Triptans: e.g. sumatriptan

4. Cyproheptadine (5HT2A antagonist) may be used in moderate to severe cases. The initial dose is 12 mg followed by 2 mg every 2 h, or 4–8 mg every 6 h if the patient remains symptomatic.

Most patients improve within 24 h of stopping the offending agent(s). Severe cases should be managed in an intensive care setting.

Evidence base

There are no RCTs investigating the management of this condition, thus treatment recommendations are based on expert consensus.

Tremor

Tremor is a common side effect of several medications. The tremor typically resembles an essential tremor, parkinsonian tremor, or a combination of the two, depending on the mechanism/s of action of the offending agent. It can occur acutely, where the presence of tremor and its severity may match drug pharmacokinetics, or in a subacute/chronic fashion which is referred to as a tardive tremor. Potential risk factors include an alternative underlying cause for tremor, older age, polypharmacy, and high-dose, immediate-release preparations which reach high serum levels. Potential drug causes of tremor are listed in Table 21.12.

Management

Management can be difficult, particularly if the tremor is tardive or if the medication cannot be withdrawn. In general, the offending medication should be reduced or withdrawn. Patients should be cautioned to reduced caffeine, alcohol, and nicotine intake as these may all exacerbate tremor. If drug withdrawal is not possible then patients with an essential tremor phenotype can be treated with a β-blocker: propranolol or metoprolol. This may be effective in up to 50% of patients.[9] In parkinsonian tremors anticholinergics can be considered and tetrabenazine may be trialled in tardive tremors.

Table 21.12 Drugs reported to cause tremor

Amiodarone
Anticonvulsants (lamotrigine, sodium valproate)
Antidepressants
Antipsychotics
Cyclosporine
Lithium
Metoclopramide
Sympathomimetics (e.g. bronchodilators, theophylline, pseudoephedrine)
Tacrolimus
Thyroxine

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Chapter 22

Neurogenetics

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Introduction

The human genome contains 3 billion nucleotide base-pairs, coding for approximately 30 000 genes. These genes are transcribed to produce RNA, which are able to leave the nucleus to be translated into proteins. Proteins are the molecular machines of life. Defects anywhere along this path can result in disease.

Following completion of the human genome project, and advances in gene sequencing, a number of previously poorly understood neurogenetic disorders have been defined and their pathogenic mechanisms elucidated. This has led to the development of disease modifying, and potentially curative, treatments for previously untreatable disorders.

Neurogenetic diseases may be divided into monogenic and polygenic disorders. Monogenic disorders result from a defect in a single gene, with dominant or recessive Mendelian or X-linked inheritance. Polygenic disorders result from the combined effects of low-impact variants found in multiple genes and environmental factors.

Approximately 4000 rare monogenic disorders have been characterized. These disorders tend to be better understood than polygenic disorders, facilitating the successful development of new treatments. Nonetheless, successful therapies still do not exist for most monogenic disorders, although multiple agents have been through clinical trials, which are ongoing. Those monogenetic neurological disorders with currently available therapies or therapies in the later stages of development are listed in Table 22.1.

Table 22.1 The state of treatment trials for monogenetic neurological disease

Disease	Inheritance	Gene	Stage of development and notable candidates
Huntington's disease (HD)	AD	*HTT* (Chr4)	Clinical Tominersen–ASO againstpathological HTT mRNA Trials were halted due to lack of efficacy, but have been restarted in a subgroup of patients that may have shown responsiveness AMT-130 consists of an AAV5 vector carrying an artificial micro-RNA specifically tailored to silence the Huntington gene

Table 22.1 (*Contd.*)

Disease	Inheritance	Gene	Stage of development and notable candidates
Neurofibromatosis type 1 (NF1), type 2 (NF2) and schwannomatosis	AD	Type 1[17] Type 2[22] Schwannomatosis[22]	Preclinical
Facioscapulohumeral muscular dystrophy (FSHD)	AD / De novo	*DUX4*	Preclinical Studies with ASOs and decoy nucleic acid
Myotonic dystrophy type 1 (DM1), type 2 (DM2)	AD	*DMPK* (CTG) *ZNF9* (CCTG)	Preclinical Oligonucleotide based therapy (ISIS 486178, AOC1001, FORCE- DMPK, Pip6a-PMO, NTC0200, Arthex-01) Gene therapy (AAV-PIN-dCas9, AAV-CRISPR-Cas9)
Oculopharyngeal muscular dystrophy (OPMD)	AD	*PABPN1* (GCG)	Preclinical Gene therapy—BB-301 (DNA directed RNA interference)
Hereditary Neuropathy with liability to pressure palsies (HNLPP)	AD	*PMP22* 17	Preclinical No genetic therapies studied to date
McArdle's disease	AR	*PYGM* 11	Preclinical Gene therapy candidates for PYGM replacement
X-linked adrenoleukodystrophy (X-ALD)	XLR	*ABCD1* (X)	Clinical Gene therapy: ALD-102 (lentiviral-based gene replacement therapy)

(*Continued*)

Table 22.1 (*Contd.*)

Disease	Inheritance	Gene	Stage of development and notable candidates
Hereditary spastic paraplegia (HSP)	AD, AR, XLR	Multiple *SPG4*	Preclinical No genetic therapies studied to date
Friedreich's ataxia (FA, FRDA)	AR	*FXN*	Clinical and preclinical ASOs (preclinical studies underway), HDACi (nicotinamide—vitamin B_3 in late-stage clinical trials), gene therapy
			(preclinical studies underway to replace dysfunctional gene), synthetic transcription factors (SynTFs—attempting to promote transcriptional elongation)
Cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL)	AD	*Notch3*[19]	Preclinical Exon-skipping ASOs
Dravet syndrome	AD	*SCN1A*	Preclinical Gene therapy (EXT101—AAV mediated gene therapy)
GLUT1 deficiency	AR	*SLC2A1*	Preclinical Gene therapy studies underway
Spinocerebellar ataxia (SCA)	AD, AR, XL	*CAG*	Preclinical Gene therapy and gene silencing (ASO, siRNA, miRNA) studies underway

Novel therapeutic agents

Several new classes of therapeutic agents have been developed for diseases with a defined genetic locus, acting at, or near, the level of DNA or RNA.

Antisense oligonucleotides (ASOs)

ASOs are short, synthetic, single-stranded DNA molecules that can alter RNA processing and influence translation into protein through several distinct mechanisms.[1]

ASOs can bind to target RNAs through complementary base pairing and form RNA–DNA hybrids. RNA–DNA hybrids are considered to be harmful to the cell and degraded by the endogenous enzyme RNase H. ASOs can also prevent the docking of ribosomal proteins, preventing translation of mRNA to protein. They may also bind to untranslated regions (UTR) of RNA to prevent binding of RNA processing proteins. They can bind to splice sites or to exon or intron inclusion signals sites, resulting in skipping or inclusion of exons, and they may increase protein translation by binding to the upstream open reading frame (ORF).

Gene therapy

Another promising avenue of disease modification, and potentially cure, is the use of gene therapy technology.

A ‘wild-type’ or ‘normal’ variant of the faulty gene is packaged into a non-pathogenic virus and administered intravenously or intrathecally. Depending on the virus used, the replacement gene may then either integrate into the patient’s genome (e.g. lentivirus) or function as a free-floating DNA circle within the nucleus (e.g. adeno-associated virus, AAV), resulting in the production of the RNA and protein that is lacking in the disease state.

A promising example is the gene therapy being trialled for Dravet syndrome, a childhood genetic epilepsy related to mutations in *SCN1A*.[2] An AAV-mediated delivery of the functional *SCN1A* gene was shown in preclinical trials in mice to increase levels of functional SCN1A in GABAergic interneurons and reduce the frequency and severity of seizures. There was also a reduction in the risk of sudden unexpected death in epilepsy (SUDEP). Treated mice with the disease mutation survived as long as mice without the disease mutation.[3]

Histone deacetylase inhibitors (HDACi)

These are a novel group of agents that are being trialled in several genetic diseases. They act at an epigenetic level, altering genetic expression without changing the underlying genetic code. This is done by blocking enzymes (deacetylases) that remove DNA-associated protein (i.e. histones) modifications. These modifications determine the ability for a cell to access and read an area of the genome.

Nicotinamide is an HDACi, which has shown promise in preclinical and early-stage clinical studies of Friedreich’s ataxia. It has been shown to increase the production of frataxin mRNA from the diseased gene, which is pathologically epigenetically silenced.[4]

Monogenic neurogenetic disorders

Below are discussed a number of conditions where genetic therapies are either used in practice or are in late-stage clinical trials. Many more are likely to emerge over the next few years.

Friedreich's ataxia (FA)

Clinical course

FA usually presents in late childhood with ataxia. Delayed motor milestones may be noted in early life. It is a multisystem disorder that most significantly affects the central and peripheral nervous system, heart, and pancreas. Patients are often wheelchair-bound within 20 years of diagnosis. The commonest cause of premature death is cardiac failure secondary to cardiomyopathy.

Genetics

FA is the result of a mutation within the gene *frataxin (FXN)*. Most of the mutations are trinucleotide repeats (GAA) that occur within the first intron of the gene. To develop the disease, a majority of patients are homozygous for the triplet repeat expansion, or they harbour one repeat expansion on one frataxin allele and a mutation on the other allele that results in loss-of-function (compound heterozygous). The presence of the intronic mutation results in partial silencing of the allele, wherein there is reduction for frataxin RNA produced, and subsequently reduced frataxin protein.[5]

The retained ability to produce frataxin despite the mutation has led to numerous avenues of therapeutic investigation attempting to increase endogenous RNA production, increase protein half-life, prevent protein degradation, and introduce exogenous genes and proteins.[5] Other treatments have been trialled to correct the downstream effects of frataxin deficiency, such as supporting mitochondrial function. The Food and Drug Administration (FDA) recently (February 2023) approved omaveloxolone as a treatment for FA, which is an Nrf2 inducer that has been shown to improve mitochondrial function and slow disease progression.[6] See drug monograph p. 662.

Genetic treatments

Trials are underway attempting to reactivate the dysfunctional gene with epigenetic compounds and deliver a frataxin minigene associated with AAV.

Huntington's disease (HD)

Clinical course

Most HD cases present in early adulthood although the age of onset can vary depending upon the number of triplet repeats present in the Huntington gene and epigenetic factors such as paternal imprinting. A larger number of repeats and paternal inheritance lead to an earlier age of disease onset.[7] Motor and non-motor features are exhibited in HD with some non-motor features now being thought to be present long before motor features manifest ('premanifest HD').[7] Motor symptoms include involuntary choreiform movements and rigidity of the body that may begin in a localized manner. Often patients have little insight into the movements. The non-motor features include impulsivity, aggression, apathy, memory impairment, insomnia, and dysphagia (which is both motor and non-motor). Symptom based treatments are discussed further in the hyperkinetic movement disorder chapter, p. 189.[7]

Genetics

HD results from a mutation within the Huntington gene (*HTT*). It is inherited in an autosomal dominant manner, and therefore only one of the two copies of the *HTT* gene needs to be mutated. The mutation is a trinucleotide repeat (CAG)n within exon one of the HTT gene. CAG repeats result in a polyglutamine (polyQ) sequence of amino acids that subsequently result in protein fragment aggregation.[7] Many other polyQ disorders have been identified to date (SBMA, DRPLA, SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17).[8]

Genetic treatments

In preclinical studies ASOs were shown to reverse clinical phenotype and HD pathology.[9,10] Unfortunately, several ASO trials have been terminated due to the poor performance of candidate ASOs (both nonselective for the CAG expanded allele and selective of certain populations of patients with CAG expansion-associated single nucleotide polymorphisms (SNPs).[11] Further trials of selective ASOs are underway.

Motor neuron disease (MND)/Amyotrophic lateral sclerosis (ALS)

Clinical course

See Chapter 9, Motor neuron disease, p. 135.

Genetics

90% of ALS cases are sporadic and show no genetic linkage.[12] The other 10% show familial inheritance in an autosomal dominant, recessive, or X-linked manner.[12] Several disease-related genes have been identified. The most common genetic causes are related to chromosome 9 open reading frame 72 (C9ORF72) (over 30%) and superoxide dismutase (*SOD1*) mutations (20%).[12] C9ORF72 mutations are also the most frequent genetic cause of frontotemporal dementia (FTD).[12] C9ORF72 mutations are hexanucleotide repeats (GGGGCC) that occur within the gene. There are three transcript variants of this gene that result in two protein isoforms.

The exact pathogenic mechanism from SOD1 mutations is not known but a toxic gain-of-function is considered most likely.[12] SOD1 detoxifies superoxide radicals, a by-product of oxidative phosphorylation, to hydrogen peroxide and oxygen, which are converted to water and oxygen by catalase and glutathione peroxidase enzymes.[12]

Genetic treatments

The first in-human study of an ASO was for SOD1-ALS, with early phase studies showing a reduction in SOD1 protein within the CSF.[13] The FDA has recently granted accelerated approval for tofersen based on improvements in surrogate endpoints that may suggest clinical improvement.[14] A phase 3 randomized, double-blind, placebo-controlled trial is ongoing in individuals who are asymptomatic carriers of the SOD1 genetic mutation.[13]

Spinal muscular atrophy (SMA)

Clinical course

SMA is an autosomal-recessive neuromuscular disorder with degeneration of alpha motor neurons leading to progressive muscular weakness and atrophy. The clinical phenotype is classified into three main subtypes, ranging from mild to severe depending on the age of onset and achieved motor abilities. The incidence approaches 1:10 000 live births. The most severe subtype: SMA type I accounts for 60% of cases.[10]

Genetics

SMA results from mutations in the *survival of motor neuron 1 gene (SMN1)* on chromosome 5q13.[15] Loss of the SMN protein results in death of motor neurons in the spinal cord and brainstem. SMN2 is a paralog (gene copy) of SMN1 and exists in multiple copies. When transcribed however, SMN2 undergoes aberrant splicing and 90% of SMN2 mRNA lack exon 7 and produces a shortened unstable protein.[15] The rescue of this aberrant transcript is the mechanism of the first FDA-approved treatment for SMA.[16]

Genetic treatments:

The ENDEAR study (n = 122) and the CHERISH study (n = 126) were phase 3 trials that evaluated the efficacy of the ASO nusinersen in infantile onset (<6 months old) and later onset (2–12 years old) SMA. Each trial was halted early to permit treatment of the control arm, as the study drug gave early signals of efficacy.[16,17]

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)

Clinical course

See Chapter 10, Disorders of muscle, p. 141.

Genetics

DMD is an X-linked recessive disease resulting from mutations in the *DMD (dystrophin)* gene. BMD is a milder form of muscular dystrophy also associated with mutations in *DMD*. *DMD* is the largest known human gene with 79 exons. The commonest cause of disease is through deletion of one or more exons.[18]

Genetic treatments

Four ASOs (eteplirsen, golodirsen, viltolarsen and ataluren) have been approved (ataluren is not approved by the FDA) as treatments for DMD. They act through exon-skipping and produce a truncated but functional dystrophin protein (see Table 22.2).[19–25] Approval was based on dystrophin protein level restoration, and not slowing of clinical progression.[19]

Delandistrogene moxeparvovec (Elevidys®) is the first AAV gene therapy approved for DMD in ambulatory children from four to five years of age. It was approved on the basis of increased expression of micro-dystrophin in treated subjects. Maintenance of approval is contingent on clinical efficacy being demonstrated in a clinical trial, which is ongoing.[20]

Table 22.2 Duchenne muscular dystrophy—approved ASO therapies

Name	References
Eteplirsen[26] 30 mg/kg once a week by intravenous infusion over 35 to 60 min Mechanism of action: Exon 51 skipping (13% of total DMD population)	FDA approved for proven exon 51 skipping DMD. Eteplirsen (Brand name: Exondys 51®) Evidence base: FDA approval was based on two phase 2 trials. Trial 1 was a 24-week placebo-controlled trial ($n = 12$, age 7–13). Each arm ($n = 4$) received either placebo, 30 mg/kg or 50 mg/kg. Followed by trial 2 a 24-week open-label extension with placebo patients switched to 30 or 50 mg/kg at week 25. At 48 weeks, those assigned to eteplirsen 50 mg/kg walked a significantly greater distance in the 6-min walk test (6MWT) compared with the placebo/delayed-start eteplirsen group. However, two patients assigned to eteplirsen 30 mg/kg lost ambulation during the trial. At 24 weeks, muscle biopsy of eteplirsen 30 mg/kg group had an increase in dystrophin-positive fibres of 23% compared with no increase in the placebo group ($p \leq 0.002$). (Muscle biopsy was not done at 24 weeks for the eteplirsen 50 mg/kg group). At 48 weeks, the increase in dystrophin-positive fibres for the eteplirsen 30 mg/kg and 50 mg/kg groups was 52% and 43%, respectively. Through week 48, there were no adverse events related to eteplirsen treatment. Since FDA approval, a larger phase-3, multicentre open-label cohort study has concluded (PROMOVI: treatment arm $n = 78/79$ completed, external controls were used as the study controls were deemed inappropriate due to baseline genetic differences in DMD). PROMOVI showed that over 96 weeks of treatment with 30 mg/kg, clinically notable reduction of decline on the 6MWT and significant reduction of per cent predicted forced vital capacity annual decline (PROMOVI: –3.3%, phase 2 studies: –2.2%, external controls: –6.0%; $p<0.001$).

(*Continued*)

Table 22.2 (*Contd.*)

Name	References
Golodirsen[27] 30 mg/kg once a week by intravenous infusion over 35 to 60 min Mechanism of action: Exon 53 skipping (8–10% of total DMD population)	FDA approved for proven exon 53 skipping DMD. Golodirsen (Brand name: Vyondys 53®) Evidence base: Study 1 Part 1 was a double-blind, placebo-controlled, dose-titration study (n=12). Patients were randomized 2:1 to receive golodirsen or matching placebo. Part 2 was a 168-week, open-label study assessing the efficacy and safety at a dose of 30 mg/kg/week in the 12 patients enrolled in Part 1, plus 13 additional treatment-naive patients. Mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 of Study 1 Part 2, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels (p <0.001); the median change from baseline was 0.88%.
Viltolarsen[28] 80 mg/kg once a week, given by intravenous infusion over 60 min Mechanism of action: Exon 53 skipping (8–10% of total DMD population)	FDA approved for proven exon 53 skipping DMD. Viltolarsen (Brand name: Viltepso®) Evidence base: 2 studies led to FDA approval. The first was a 4-week dose-finding safety trial in USA and Canada (n = 16, 3:1 iv vitolarsen 40 mg/kg or 80 mg/kg to placebo) followed by 20-week open-label treatment. Patients assigned to viltolarsen 80 mg/kg once a week showed an increase in dystrophin levels in muscle biopsies from a mean level of 0.6% of normal at baseline to 5.9% of normal at week 25. Among secondary outcomes, all 16 subjects showed improvement on timed function tests compared with historical controls. The second study was a similar trial that was conducted in Japan for 24 weeks.
Ataluren[29,30] The recommended dose is 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening, for a total daily dose of 40 mg/kg. Recommended dosing intervals are 6 h between morning and midday doses, 6 h between midday and evening doses, and 12 h between the evening dose and the first dose on the following day. Mechanism of action:	Not FDA approved. Approved for use in the UK and Europe. Ataluren (Brand name: Translarna®) Evidence base: Efficacy was assessed in two multicentre double-blind randomized trials with change in 6 metre walk distance (6MWD) at 48 weeks. Study 1 included 174 ambulatory males (median age 8 years, range 5–20) with nmDMD to high-dose ataluren (80 mg/kg/day), low-dose ataluren (40 mg/kg/day), or placebo TID. At 48 weeks, the mean decline in the 6MWD was approximately 30 metres less for the low-dose group compared with the placebo group. There was no significant difference between the high-dose group and placebo.

Table 22.2 (*Contd.*)

Name	References
For DMD patients >2yo caused by nonsense mutations (nmDMD) (10–15% of total DMD population)	Study 2 (ACT DMD) of 228 boys with nmDMD, found no significant benefit of ataluren for the primary endpoint 6MWD, though there was benefit for some secondary endpoints. European approval was gained based on the findings of the low-dose ataluren group. The FDA has not approved ataluren in the USA. European approval was gained based on the findings of the low-dose ataluren group. The FDA has not approved ataluren in the USA. Interim analysis of real-world use since 2015 to 2022 in the STRIDE study (n = 307 from 14 countries) found that standard of care alongside ataluren use (mean 1671(SD 566.8) days) resulted in delay in loss of ambulation by 4 years (p <0.0001). A trend towards improved respiratory function was also shown, with subsequent longitudinal analysis, or increase in sample size needed to assess a more statistically meaningful analysis.

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Drugs

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Chapter 23

Drug classes

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Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (AChEIs), also known as anticholinesterases, are a large group of drugs that bind to and inhibit cholinesterase, which degrades acetylcholine, thereby elevating levels of acetylcholine within the synaptic cleft. Only reversible AChEIs are used therapeutically. Irreversible AChEIs are highly toxic and are used as insecticides and in chemical warfare. Reversible AChEIs are used in the symptomatic management of neuromuscular junction (NMJ) disorders and dementia, most commonly Alzheimer's disease (AD).

Uses

Three reversible cholinesterase inhibitors, edrophonium, neostigmine, and pyridostigmine, are currently used for the treatment of NMJ pathology. Pyridostigmine is the most widely used AChEI for this indication, as it has the longest duration of action and superior side effect profile. Edrophonium and neostigmine have shorter durations of activity. Edrophonium has such a short half-life that it is predominantly used as a diagnostic test for myasthenia gravis (MG) (the Tensilon® test). Neostigmine is four times as potent as pyridostigmine and hence has more pronounced cholinergic side effects.

Other reversible AChEIs, which can cross the blood–brain barrier, such as donepezil, galantamine, and rivastigmine, are licensed for use in the treatment of mild-to-moderate AD. They are also often used for Lewy body and Parkinson's-associated dementia. These medications differ in terms of their pharmacokinetics, their specificity for acetylcholinesterase, and their affinity for acetylcholinesterase in different parts of the central nervous system (CNS). This may contribute to differences in their efficacy and side effect profiles. The advantages and disadvantages of different AChEIs used in dementia are given in Table 23.1.

Mechanism of action

- *NMJ disorders*: reversible inhibition of cholinesterase serves to increase synaptic concentrations of acetylcholine, potentiating the action of acetylcholine on muscarinic and nicotinic acetylcholine receptors (AChRs). The former group of receptors contribute to the side effect profile, and the latter to the therapeutic effect.
- *Dementia*: AChEIs were initially developed on the basis of the 'cholinergic hypothesis', i.e. post-mortem studies of the brains of patients with AD were found to be deficient in acetylcholine. In light of increased knowledge of the pathology of AD, this is now felt to be an oversimplification. AChEIs are thought to exert their beneficial effects in a number of ways, including activation of neurotrophic mechanisms, modulation of amyloid plaque and neurofibrillary tangle synthesis, and potentially by protecting the brain from glutamate-induced excitotoxicity. In addition to anticholinesterase activity, donepezil independently interacts with neuronal nicotinic AChR; rivastigmine forms temporary covalent bonds with the AChR, and galantamine may enhance the intrinsic action of acetylcholine on nicotinic receptors. The clinical significance of these variations in activity profile is unclear.

Table 23.1 A comparison of AChEIs used in the treatment of dementia

	Preparations	Advantages	Disadvantages
Donepezil	Orodispersible, solution, and standard tablet	Renal impairment is not a contraindication; beneficial effects on behaviour; orodispersible formulation aids compliance	Potential for drug interactions by CYP450 enzyme inhibitors/ inducers
Galantamine	Oral solution, prolonged-release capsules and tablets, and standard tablets	Prolonged-release versions allow od dosing. Least expensive treatment for AD	Cautionary use in hepatic impairment and potential for drug interactions by CYP450 enzyme inhibitors or inducers
Rivastigmine	Capsules, oral solution, and patch	Available as a patch, no interaction with CYP450 enzyme inhibitors/ inducers, beneficial effects on behaviour, and licensed in PDD (and DLB in UK)	May be associated with more gastrointestinal side effects than donepezil

Toxicity and side effects

Side effects shared by all cholinesterase inhibitors:

- *Common—gastrointestinal*: abdominal cramps, diarrhoea, dyspepsia, increased salivation, nausea, vomiting, and weight loss. *Urological*: incontinence.
- *Serious—cardiovascular*: arrhythmias, bradycardia, heart block, hypotension, and syncope.
- *Cholinergic crisis*: with overdose, there is a risk of cholinergic crisis developing as a result of a depolarizing neuromuscular blockade. This can cause potentially lethal bulbar and respiratory muscle weakness. It is important to distinguish this from a worsening myasthenic crisis, as management is very different. The Tensilon® test may help differentiate the two.

Side effects shared by donepezil, galantamine, and rivastigmine:

- *Common—Anaesthesia:* exaggerated muscle relaxation with succinylcholine *Musculoskeletal*: arthralgia and muscle cramps. *Neurological*: dizziness, fatigue, headache, insomnia, and weakness.

Pulmonary—dyspnoea. Psychiatric: abnormal dreams, agitation, depression, and hallucinations.
- *Serious—gastrointestinal*: hepatitis and gastric/duodenal ulcers. *Haematological*: anaemia and thrombocytopenia with galantamine. *Neurological*: seizures and worsening of symptoms of PD. Neuroleptic malignant syndrome (NMS) has been reported with donepezil and rivastigmine use.

Side effects shared by edrophonium, neostigmine, and pyridostigmine:
- *Serious*—neurological: paralysis and weakness. Respiratory: bronchoconstriction and increased bronchial secretions.

Contraindications

Contraindications shared by all acetylcholinesterase inhibitors:
- *Absolute*: hypersensitivity to the individual drug or its excipients. AChEIs should not be given to patients with mechanical intestinal or urinary obstruction.
- *Relative*: caution is advised in patients with bronchial asthma and chronic obstructive pulmonary disease (COPD), co-morbid bradycardia, arrhythmia, sick sinus syndrome, peptic ulcer disease, epilepsy, and parkinsonism.

Contraindications shared by edrophonium, neostigmine, and pyridostigmine: Hyperthyroidism and recent coronary artery occlusion. In patients with chronic kidney disease, elimination of AChEI may be prolonged; hence dose reduction may be required. No dose alteration is required in hepatic failure.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens. The elderly are also more likely to get neuropsychiatric side effects and worsening renal function; hence urea and electrolytes (U&Es) should be frequently monitored. The elderly are also more prone to sinus bradycardia and cardiac conduction defects.
- *Pregnancy*: limited data are available regarding the use of acholinesterase inhibitors in pregnancy. Limited evidence from human exposure suggests pyridostigmine is not a major teratogen. There is no significant data for the other medications in humans. Use with caution if potential benefits outweigh the risks.
- *Lactation*: Pyiridostigmine is present in breast milk, but levels are very low, infants are estimated to receive a maximum of 0.1% of the maternal dose and so breastfeeding is not contraindicated. Neostigmine was not detected in the breast milk of mothers taking the medication. Edrophonium is unlikely to be present in breastmilk. Given its short half-life, waiting 2–3 h after administration would minimize any possible risk of affecting the infant. There is minimal data on the use of centrally acting acetylcholinesterase inhibitors. They are likely to be present in breast milk, leading manufacturers to recommend avoiding breastfeeding if mothers are taking the medication.

Efficacy

Centrally acting acetylcholinesterase inhibitors for Alzheimer's dementia:

- *Donepezil*: a 2006 Cochrane review of donepezil use in AD (*n* = 5769, from 24 RCTs) concluded that cognition, assessed with the ADAS-Cog scale, improved with donepezil use at 24 weeks. For 5 mg and 10 mg doses, there was an improvement of −2.01 points mean difference (95% CI −2.69 to −1.34; $p < 0.00001$) and −2.80 points mean difference (95% CI −3.74 to −2.10; $p < 0.0001$), respectively, compared with placebo. The study also concluded that there was a non-significant improvement of 1.84 points in the mini mental state examination (MMSE) score at 52 weeks, when compared to placebo (95% CI 0.53–3.15; $p = 0.006$). Studies suggest that there is marked inter-patient variability in patients' response to donepezil. However, there are as yet no indicators to predict the extent of response in individual patients.
- Evidence from open-label extension trials of up to 3 years suggests that the rate of cognitive decline in treated patients may be less than that of untreated patients. In addition, donepezil has also been shown to reduce non-cognitive features of AD, such as low mood, hallucinations, and delusions, in mild-to-moderate disease. A trial of 10 mg vs. 23 mg donepezil in patients with moderate-severe AD did not show a significant difference in global functioning. Although post-hoc analyses have suggested some benefit in more severe AD, for some of the ratings scales used (see Chapter 14). Patients taking the higher dose developed a higher incidence of dizziness and gastrointestinal (GI) side effects.
- *Galantamine*: a 2014 meta-analysis of three placebo-controlled trials of galantamine in patients with mild-to-moderate AD showed a pooled weighted mean difference (WMD) in change between intervention and placebo of −3.03 (95% CI −3.66 to −2.41) and −3.2 points (95% CI −3.28 to −3.12) in the ADAS-Cog score at 24 mg and 32 mg doses of galantamine, respectively. Current head-to-head trials have not shown a difference when comparing galantamine to donepezil. Adjusted indirect comparison studies suggest that non-cognitive features, such as behaviour, respond better to donepezil and rivastigmine than galantamine, and that, in general, galantamine is not as well tolerated when compared to other AChEIs.
- *Rivastigmine*: in 2009, the Cochrane collaboration systematically reviewed the use of rivastigmine in mild-to-moderate AD. They included nine double-blind, placebo-controlled, randomized trials of 4775 patients receiving 6–12 mg of rivastigmine and showed a 2-point improvement in cognitive function on the ADAS-Cog score vs. placebo (WMD −1.99, 95% CI −2.49 to −1.50; $p < 0.00001$) at 26 weeks. A 2.2-point improvement in the activities of daily living, assessed on the Progressive Deterioration Scale, was also seen (WMD −2.15, 95% CI −3.16 to −1.13). In severe AD, several randomized, placebo-controlled trials showed a reduction in cognitive decline in moderately severe (Geriatric Depression Scale (GDS) less than or equal to 5) AD. Mean change from baseline ADAS-Cog scores was significantly improved in patients receiving 6–12 mg/day of rivastigmine (2.3, 95% CI 0.09–3.84;

p <0.001) and 1–4 mg/day of rivastigmine (−1.2, 95% CI −2.61 to 0.31; p <0.001) at 26 weeks in one placebo-controlled trial of 159 patients.

Centrally acting acetylcholinesterase inhibitors for Lewy body dementia

- A 2012 Cochrane review assessed the use of AChEIs in PDD and DLB (1236 participants in six randomized, placebo-controlled trials). An improvement in cognitive function, as measured by MMSE scores, was noted for PDD (mean difference 1.09, 95% CI 0.45–1.73; p = 0.0008), but not for DLB. In PDD, cholinesterase inhibitors were also demonstrated to have a positive effect on behavioural assessment and activities of daily living, with no significant impact on Unified Parkinson's Disease Rating Scale (UPDRS) scores. The Cochrane review concluded that the effects in DLB remained unclear.

Peripherally acting acetylcholinesterase inhibitors for neuromuscular junction disorders:

- *Edrophonium*: the edrophonium test for diagnosing MG is positive if a substantial improvement in muscle power occurs in an objectively visible muscle group after injection of edrophonium, most commonly interpreted by resolution of ptosis. The test has a sensitivity of 95% for generalized MG, although a variety of neuromuscular disorders, such as Lambert–Eaton myasthenic syndrome (LEMS), can yield a false-positive result. The Tensilon® test may also aid in the distinguishment of a cholinergic crisis from a myasthenic crisis.
- *Neostigmine*: there have been no good-quality RCTs regarding the use of neostigmine in MG, other than one small and inconclusive trial using intranasal neostigmine in ten participants. Nonetheless, there is a wealth of clinical observational experience which points to the efficacy of neostigmine in treating MG. Its side effect profile and relatively short duration of action means it is less frequently used when compared to pyridostigmine.
- *Pyridostigmine*: although there are no randomized, placebo-controlled trials of the use of oral pyridostigmine in the treatment of MG, there is a wealth of clinical observational evidence which points to its efficacy. As such, guidelines state that pyridostigmine is the first-line treatment for all forms of MG, with the caveat that patients with anti-MuSK antibodies likely have a reduced benefit when compared to Acetylcholine receptor antibody (ACRA) positive patients.

Dosing and monitoring

Dosing

Centrally acting acetylcholinesterase inhibitors for dementia:

- *Donepezil*: start treatment at 5 mg od at night. This can be increased to 10 mg after 4–6 weeks. The 23 mg dose (available in the USA, not UK) can be administered to patients with severe AD, once patients have been established on 10 mg for at least 3 months.
- *Galantamine*: for oral solution and standard tablets, start treatment at 4 mg bd, increasing to 8 mg bd after 4 weeks. This can again be increased to 12 mg bd after a further 4 weeks, depending on individual

tolerability. For extended-release preparations, start treatment at 8 mg od dose, taken in the morning with food. Increase to 16 mg after 4 weeks and, if tolerated, 24 mg after a further 4 weeks.

- *Rivastigmine*: for oral rivastigmine, start treatment at 1.5 mg bd. This can be increased by 1.5 mg/dose every 2 weeks to a maximum of 6 mg bd. For transdermal preparations, start treatment with a 4.6 mg/24 h patch applied and increase to 9.5 mg/24 h patch after a minimum of 4 weeks. If well tolerated and there is evidence of benefit, this can be further increased to 13.3 mg/24 h after an additional 4 weeks. When dosing is omitted for >3 days, re-initiation at the lowest dose is recommended. Consider lowering the dose for patients with mild-to-moderate hepatic impairment.

Peripherally acting acetylcholinesterase inhibitors for neuromuscular junction disorders:

- Edrophonium:
  - *Diagnosis of MG*: a test dose of 2 mg IV is administered over 15–30 s. If no reaction is noted after 60 s, an 8 mg bolus is given into a large IV line, followed by a saline flush. If cannulation is unsuitable or unsafe, 10 mg IM can be given as an alternative. Oral cholinesterase inhibitors should be withheld for 24 h prior to testing.
  - *Assessment of treatment adequacy of MG*: a test dose of 2 mg IV is administered >1 h after the last administration of the patient's usual pyridostigmine dose. If the patient has been over-treated with pyridostigmine, administration of edrophonium will transiently worsen symptoms; conversely, if the patient has been receiving insufficient pyridostigmine, transient improvement in symptoms will be seen;
- *Neostigmine*: should be commenced at a dose of 15 mg every 3–4 h and doubled every few days, according to response and side effects, up to a maximum of 75–300 mg total daily dose. In severe disease, neostigmine can be given more frequently, usually in an inpatient setting.
- *Pyridostigmine*: start treatment at 30 mg tds, doubling every few days, according to response and side effects, up to a total daily dose of 1.2 g (UK) or 1.5 g (USA). A typical regimen is 60–90 mg every 4–6 h during the day.

Monitoring

Severe cholinergic reactions can result from the administration of edrophonium, particularly in the form of life-threatening bradycardia, arrhythmias, and hypotension. Cardiac telemetry is advised. Resuscitation facilities, particularly IV atropine (1–2 mg) for urgent reversal of bradyarrhythmia, should always be available for diagnostic procedures involving edrophonium. This is not required with other cholinesterase inhibitors, although they can cause bradycardia and heart block. Electrocardiogram (ECG) is recommended prior to and after treatment to ensure a patient is not at risk of this.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.2.
Interactions See Table 23.3.

Table 23.2 Pharmacokinetics of AChEIs

	Pyridostigmine	Neostigmine	Edrophonium	Donepezil	Galantamine	Rivastigmine
Indication	NMJ disorders			Dementia		
Administration	PO, IV	IV, PO, SC	IV, IM	PO	PO	PO, TD
Onset of action	15 min	1 min	1–2 min	NA	NA	NA
Duration of action	360 min	20–30 min	10 min	NA	3 h	NA
Oral bioavailability	10–20%	5%	NA	100%	88%	36%
T_{max} (h)	1–2	1–2	NA	3–4	1	1 (PO)8–16 (TD)
Affected by food	Yes	Yes	NA	No	Yes	Yes
Protein binding	81%	15–25%	NA	95%	18%	40%
Cross BBB?	No	No	No	Yes	Yes	Yes
Metabolism	Negligible	Hepatic	Cholinesterases	CYP2D6/3A4	CYP2D6/3A4	Cholinesterases
Excretion	Urine 80%	Urine 50%	75% urine; 5% bile	Urine 57%	Urine 90%	Urine >90%
Elimination half-life	3–4 h	77 min	33–110 min	70 h	7 h	1.5 h

BBB, blood–brain barrier; IM, intramuscular; IV, intravenous; NA, information not available; PO, oral; TD, transdermal.

Table 23.3 Interactions of AChEIs

Pharmacodynamic interactions

With aminoglycosides: effects of neostigmine and pyridostigmine antagonized.

With anticholinergics: diminished therapeutic effect.

With antipsychotics: enhanced neurotoxic effects, e.g. extrapyramidal symptoms (particularly donepezil and rivastigmine).

With β-blockers and other negative chronotropic agents: risk of arrhythmia and bradycardia.

With cholinergic agonists: enhanced toxicity.

With non-depolarizing neuromuscular blockers: AChEIs reduce neuromuscular-blocking effect.

With depolarizing neuromuscular blockers: AChEIs enhance neuromuscular-blocking effect.

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α2-adrenergic agonists

α2-adrenergic agonists are often used in individuals with Tourette's syndrome (TS), particularly if they have co-morbid attention deficit hyperactivity disorder (ADHD). The newer agent guanfacine is presumed to be better tolerated than clonidine; however, definitive comparative studies are lacking.

Uses

Licensed uses

In the UK/USA

1. ADHD as monotherapy and as adjunctive therapy to stimulant medications.

Off-label uses

1. Clonidine: tics and TS.
2. Guanfacine: tics and TS.

Mechanism of action

Clonidine and guanfacine are centrally acting α2 receptor agonists. The α2-adrenoceptor is autoinhibitory and therefore inhibits the firing of noradrenergic neurons in the CNS. Clonidine has non-specific activity at α2A, B, and C receptors, as well as imidazoline receptors, while guanfacine preferentially binds α2A receptors. Their action in the locus caeruleus is thought to reduce sympathetic activity, resulting in their antihypertensive effect. The mechanism behind their beneficial effects in the management of tic disorders are less clear, although animal studies suggest that tic suppression and improved attention may be the result of improved connectivity of prefrontal cortical networks.

Toxicity and side effects

- *Common*—*Cardiovascular*: bradycardia. *Dermatological*: application site reaction (transdermal clonidine). *Gastrointestinal*: anorexia, constipation, decreased appetite, dry mouth, elevated LFTs (alanine aminotransferase

(ALT)), nausea, and vomiting. *Musculoskeletal*: weakness. *Neurological*: dizziness, drowsiness, fatigue, and headache.
- *Serious—Cardiovascular*: arrhythmias, atrioventricular (AV) block, cardiac failure, myocardial infarction (MI), rebound hypertension, and tachycardia. *Dermatological*: exfoliative dermatitis. *Gastrointestinal*: colonic pseudo-obstruction. *Neurological*: convulsions and stroke. *Ophthalmological*: iritis. *Psychiatric*: hallucinations and mania.

Contraindications

- *Absolute*: known hypersensitivity to the drug or its constituents.
- *Relative*: bradycardia due to second- or third-degree AV block. Use with caution in patients with cardiovascular, cerebrovascular, or peripheral vascular disease and Raynaud's syndrome. Dose adjustment is advised in severe hepatic or renal impairment for both agents. Use the lowest effective dose and assess for side effects which are more likely in patients with renal and liver disease (bradycardia, sedation, and hypotension).

Use in special populations

- *Elderly*: no specific dose alterations are routinely required. Caution should be taken, as the elderly experience an age-related decline in renal and hepatic function and may be more prone to cardiovascular side effects.
- *Pregnancy*: limited data are available for the safety of these agents in pregnancy. Clonidine can cross the placenta and may lower foetal heart rate. The use of these agents in pregnancy should only be considered, if essential.
- *Lactation*: clonidine is present in breast milk; it is not known if guanfacine is too. In limited studies, serum levels of clonidine have reached ~50% of simultaneous maternal levels and infant side effects have been reported. The manufacturers advise avoidance in nursing mothers where possible.

Efficacy

A meta-analysis of six RCTs found α2-agonists to be beneficial in treating tic disorders in children (SMD = 0.31, 95% CI 0.15–0.48; $p < 0.001$). However, subgroup analysis identified the greatest efficacy in children with concomitant ADHD, and minimal benefit in those without ADHD. Significant publication bias is reported, based on funnel plot analysis. Correction for this still resulted in moderate, yet still significant, efficacy (SMD = 0.18, 95% CI 0.03–0.33). Comparative subgroup analysis showed no significant difference in efficacy between clonidine and guanfacine ($p = 0.44$). This may be the result of a relative lack of guanfacine trials.

Dosing and monitoring

Dosing

1. *Clonidine*: start treatment at 25–50 micrograms/day, and increase every 2–3days by 25–50 micrograms/day. The normal maintenance dose is 100–300 micrograms/day, in 2–3 divided doses.
2. *Guanfacine*: start treatment with the standard-release preparation at 0.5 mg od at night for 3 days, then increase to 0.5 mg bd for 4 days,

and then to 0.5 mg tds after a further week. This can be increased, as required, to 0.75–3 mg/day in three divided doses.

Monitoring
Consider ECG at baseline if there are risk factors or known cardiovascular disease. Treatment should be withdrawn gradually, due to the risk of rebound hypertensive crisis.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.4.
Interactions See Table 23.5.

Table 23.4 Pharmacokinetics of α2-adrenergic agonists

	Clonidine	Guanfacine
Main routes of administration	PO/TD	PO
Bioavailability	70–80% (TD: 60%)	80–100%
T_{max}	1–3 h	1–4 h
Protein binding	30–40%	64%
Metabolism	Hepatic	Hepatic, mainly CYP3A4
Pharmacologically active metabolites	No	NA
Elimination half-life	12–16 h	17 h
Excretion	Urine, mainly as unchanged drug (70%), faeces (20%)	Urine ~50% as unchanged drug

NA, information not available; PO, oral; TD, transdermal.

Table 23.5 Interactions of α2-adrenergic agonists

Medications which alter plasma levels	Pharmacodynamic interactions
Guanfacine (clonidine none): levels decreased: CYP3A4 inducers, e.g. carbamazepine, phenytoin, and St John's wort levels increased: CYP3A4 inhibitors, e.g. clarithromycin and fluoxetine	With antihypertensives: increased hypotensive effect. With β-blockers and TCAs: risk of rebound hypertension on withdrawal—will need to be withdrawn slowly, if used together With β-blockers, calcium channel blockers, cardiac glycosides: may increase the risk of AV block. Clonidine (not guanfacine) with methylphenidate: some reports have suggested an increased risk of death with this combination, although causality has not been established

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Alpha-glucosidase enzyme replacement therapies

The alpha-glucosidase enzyme replacement therapies are a group of human recombinant alpha-glucosidase analogues used to treat Pompe disease. Alglucosidase alfa has been available since 2006, it has been shown to improve outcomes for individuals with both infantile and adult onset Pompe disease. Avalglucosidase has enhanced binding to mannose-6-phosphate receptors, resulting in increased uptake into target tissues. Cipaglucosidase alfa has also been modified to improve its cellular uptake and is licensed to be taken with miglustat, which stabilizes the cipaglucosidase alfa molecule, prolonging its half-life. Trials comparing the two newer therapies with alfaglucosidase alfa have demonstrated non-inferiority and a trend towards improved outcomes, but this was not statistically significant.

Uses

Licensed uses

In the UK/USA

- *Pompe disease:*

1. *Alglucosidase alfa:* Alglucosidase alfa is licensed for the treatment of Pompe disease in individuals of all ages.
2. *Avalglucosidase alfa:* Avalglucosidase alfa is licensed for the treatment of Pompe disease in individuals of all ages (UK)/aged 1 year and older (USA).
3. *Cipaglucosidase alfa (used in combination with miglustat)* is licensed for the treatment of late-onset Pompe disease in individuals aged 18 years and older. (In the USA the FDA label stipulates patients must weigh >40 kg and not be improving on their current enzyme replacement therapy).

Off-label uses

- None.

Mechanism of action

These three agents act as a replacement for the endogenous alpha-glucosidase (GAA) enzyme. Once infused each agent is internalized into lysosomes, where they undergo proteolytic cleavage to GAA, which then metabolizes glycogen. Cipaglucosidase alfa is used in combination with miglustat which binds with, stabilizes, and reduces inactivation of cipaglucosidase alfa after infusion.

Toxicity and side effects

- *Common— Dermatological:* Pruritus, urticaria, erythema. *Gastrointestinal*: Diarrhoea, nausea, vomiting. *Musculoskeletal*: Myalgia *Neurology*: Headache and vertigo. *Rheumatological*: Arthralgia.
- *Serious— Cardiological*: Fluid overload and cardiorespiratory failure. *Immunological*: Hypersensitivity reactions including anaphylaxis, infusion-associated reactions (IARs), and immune-complex related reactions.

Contraindications

- *Absolute*: Hypersensitivity to the medication or its excipients.
- *Relative*: No specific safety data is available to guide use in renal or hepatic impairment. These enzymes are metabolized by proteolytic hydrolysis in the liver, renal impairment is unlikely to affect their metabolism.

Use in special populations

- *Elderly*: No dose adjustment is necessary in the elderly population.
- *Pregnancy*: There is minimal data on the use of GAA enzyme replacement therapy (ERT) during human pregnancy. Immunological reactions lead to maternal and foetal toxicity in animal studies. Foetal toxicity is considered likely to be secondary to the maternal immunological response, as GAA ERT does not cross the placenta. The manufacturers advise avoiding cipaglucosidase alfa in combination with miglustat during pregnancy, as miglustat alone and in combination therapy has been demonstrated to have reproductive toxicity.
- *Lactation*: Limited data suggest that GAA ERT is excreted in breast milk in very low concentrations. No clinical effect is expected in a breastfed infant due to low breast milk transfer and poor bioavailability. Breastfeeding during treatment may therefore be considered, although a risk to infants cannot be excluded. As a precautionary measure, breastfeeding interruption for the first 24 h after treatment can be considered.

Efficacy

Alglucosidase alfa:

Infantile-onset Pompe disease (PD): Three clinical trials evaluated the safety and efficacy of alglucosidase alfa in 57 treatment-naïve infantile-onset PD patients. The studies demonstrated that alglucosidase alfa improves survival and motor function in these patients, and that earlier initiation of treatment is associated with better outcomes.

Late-onset PD: A randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of alglucosidase alfa in 90 patients with LOPD. The study found that alglucosidase alfa significantly improved forced vital capacity (FVC) compared to placebo after 78 weeks of treatment. The mean % predicted FVC increased from 55% at baseline to 56.2% in the alglucosidase alfa-treated group, while it decreased to 52.8% in the placebo-treated group. These findings suggest that alglucosidase alfa is an effective treatment for LOPD.

Avalglucosidase alfa: A randomized, double-blinded, multinational, multicentre trial compared the efficacy and safety of avalglucosidase alfa to alglucosidase alfa in treatment-naïve patients with LOPD. The primary endpoint was the change in FVC (% predicted) in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (% predicted) for patients treated with avalglucosidase alfa and alglucosidase alfa was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% CI: –0.1, 5) favouring avalglucosidase alfa. Superiority was not reached (p = 0.063)

Cipaglucosidase alfa (in combination with miglustat): A randomized, double-blind, parallel-group, multinational phase 3 trial (n=125) in subjects ≥18 years old diagnosed with LOPD, compared IV cipaglucosidase alfa (20 mg/kg) plus oral miglustat against a non-U.S. approved IV alglucosidase alfa (20 mg/kg) plus oral placebo, every 2 weeks for 52 weeks. The primary endpoint was change from baseline to week 52 in 6-min walk distance. At week 52, the mean change from baseline in 6-min walk distance was 20.8 m (SE 4.6) for the cipaglucosidase alfa plus miglustat group versus 7.2 m (SE 6.6) for the alglucosidase alfa plus placebo group using last observation carried forward (between-group difference 13.6 m. This was not statistically significant [95% CI −2.8 to 29.9]).

Dosing and monitoring

Dosing

Prior to treatment, consider pre-treating with antihistamines, antipyretics, and/or corticosteroids.

Alglucosidase alfa: Administer 20 mg/kg body weight every 2 weeks as an intravenous infusion.

Avalglucosidase alfa: Administer 20 mg/kg (of actual body weight) every two weeks. The initial recommended infusion rate is 1 mg/kg/h. If there are no signs of IARs, gradually increase the infusion rate every 30 min in each of the following three steps: 3 mg/kg/h, 5 mg/kg/h, and then 7 mg/kg/h; then, maintain the infusion rate at 7 mg/kg/h until the infusion is complete.

Cipaglucosidase alfa (in combination with miglustat): Administer 20 mg/kg of body weight fortnightly. The infusion should start 1–3 h after taking miglustat.

Monitoring

Prior to starting treatment, patients should undergo pulmonary function testing, echocardiography, GAA enzyme levels, anti-drug antibodies (ADA). These should be repeated at regular intervals depending on patient response and clinical need.

The results of the monitoring tests will be used to determine if the patient's ERT dosage or schedule needs to be adjusted. If the patient's condition is not improving or is deteriorating, the dosage may need to be increased or the frequency of infusions may need to be increased. If the patient is developing antibodies to a GAA ERT, a different type of ERT may be needed.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.6.

Interactions

Table 23.6 Pharmacokinetics of alpha-glucosidase ERT

	Alglucosidase alfa	Avalglucosidase alfa	Cipaglucosidase alfa
Protein binding	No	No	No
Metabolism	Not characterized, likely hepatic by proteolytic hydrolysis	Not characterized, likely hepatic by proteolytic hydrolysis	Hepatic by proteolytic hydrolysis
Pharmacologically active metabolites	No	No	No
Elimination half-life	5.4 h	1.6 h	1.6–2.6 h

No interaction studies have been performed. Given they are recombinant human proteins these agents would not be expected to react with other medicinal products.

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Anti-amyloid-β monoclonal antibodies

The anti-amyloid-β monoclonal antibodies are a new class of drug developed for the treatment of Alzheimer's disease. The FDA have approved two agents, aducanumab and lecanemab, for clinical use. There are several others in late-stage clinical testing.

Uses

Licensed uses

In the USA, (These medications are not available in the UK)

- Both aducanumab and lecanemab are licensed for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of the disease (the population in which treatment was initiated in clinical trials), in individuals aged 18 years and older.

Off-label uses:
None

Mechanism of action

Aducanumab and lecanemab are recombinant humanized immunoglobulin gamma one (IgG1) monoclonal antibodies targeting aggregated soluble oligomers and insoluble fibril conformations of Aβ plaques in the brain. Lecanemab was shown to have preferential and strong binding to Aβ protofibrils thereby preventing plaque formation, whilst aducanumab has a relatively stronger affinity for formed fibrils and binds amyloid plaques, increasing plaque clearance. This difference in binding characteristics may explain the difference in clinical efficacy and lower amyloid-related imaging abnormalities—cerebral oedema (ARIA-E) frequency seen with lecanemab as compared to aducanumab.

Toxicity and side effects

- *Common—Gastrointestinal*: Diarrhoea. *Immunological:* Infusion reaction. *Neurological*: Amyloid-related imaging abnormalities (ARIA), ARIA-E (oedema), ARIA-H (haemorrhage and superficial siderosis), confusion, and headache. *Respiratory*: cough, dyspnoea.
- *ARIA:* Both anti-amyloid antibodies can cause ARIA, which includes ARIA-E (cerebral oedema) and ARIA-H (haemorrhage and superficial siderosis). ARIA (E and H) were noted in 41% of patients given aducanumab compared to 10% of patients on placebo. Clinical symptoms (most commonly headache, confusion, and dizziness) were seen in 24% of patients who had ARIA. 0.7% of patients with ARIA had a seizure. Intracerebral haemorrhage >1 cm was seen in 0.5% of patients aducanumab and 0.4% of patients taking placebo. ARIA was noted in 12% of patients treated with lecanemab compared to 5% with placebo (including asymptomatic radiological events). One patient out of 161 patients had an intracerebral haemorrhage >1 cm whilst treated with lecanemab compared to zero with placebo ($n = 245$). Particular vigilance for ARIA is recommended during the first 8 doses of aducanumab and 14 doses of lecanemab and while the dose is being titrated. Apolipoprotein E ε4 (ApoE ε4) homozygotes had a higher risk of developing ARIA compared to heterozygotes and non-carriers. ApoE ε4 status should be collected prior to treatment to help predict the risk of developing ARIA.

Contraindications

- *Absolute:* Hypersensitivity reactions to active substance or components of the formulation.
- *Relative:* Use with caution in patients with pre-existing risk factors for intracerebral haemorrhage, including prior cerebral haemorrhage >1 cm in greatest diameter, >4 microhaemorrhages, superficial siderosis, evidence of vasogenic oedema or cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, or severe small-vessel or white matter disease. No dose alterations are required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: No dose alteration is required.
- *Pregnancy*: No data is available from human studies. Rat studies have been undertaken, however given aggregated amyloid beta is not present in rats, these are unlikely to be helpful. The manufacturer advises avoiding use in pregnancy.
- *Lactation*: No data is available from animal or human studies.

Efficacy

Aducanumab:

The approval for aducanumab was based on analyses of two double-blind phase 3 trials (EMERGE and ENGAGE) and based on noted reduction in amyloid burden on imaging. The primary endpoint was met in EMERGE but not in ENGAGE, despite both studies demonstrating a reduction in amyloid burden.

Included subjects for both studies had mild cognitive impairment (MCI) due to AD or very mild dementia due to AD (MMSE >24), Clinical Dementia Rating-Sum Of Boxes (CDR-SB) score 0.5 and positive amyloid positron emission tomography (PET) scan.

EMERGE: Subjects (n = 1638) were treated with either low dose (3 or 6 mg/kg), high-dose (10 mg/kg) aducanumab or placebo. Subjects in the high-dose arm had a smaller clinical decline and met the primary endpoint – 0.39 compared to placebo (95% CI, –0.69 to –0.09; p = 0.012; 22% decrease). Participants in the high-dose group also demonstrated less decline in secondary endpoints of scores on the MMSE (p = 0.049), ADAS-Cog13 (p =0.010), and ADCS-ADL-MCI (p <0.001) compared to placebo.

ENGAGE: The primary and secondary endpoints were not reached (n = 1647).

Lecanemab:

CLARITY AD was a phase 3 randomized controlled study (n = 1795) with subjects assigned to receive 10 mg/kg infusion of lecanemab or placebo every 2 weeks. A statistically significant treatment difference was shown in the CDR-SB score change (–0.45; p = 0.00005), indicating a reduction in clinical decline of 27% with lecanemab over 18 months compared with placebo. Findings also showed statistically significant improvements in all key secondary endpoints compared with placebo (p <0.001), including changes in amyloid levels, the ADAS-Cog14 (–1.44 [95% CI, –2.27, –0.61]), the ADCOMS (–0.050 [95% CI, –0.074, –0.027]), and the ADCS-ADL-MCI (2.0 [95% CI, 1.2–2.8]).

Dosing and monitoring

Dosing

Aducanumab:

Dosing based on actual body weight. Doses should be at least 21 days apart.
Doses 1 and 2 (weeks 0 and 4)—1 mg/kg IV over one h
Doses 3 and 4 (weeks 8 and 16)—3 mg/kg IV over one h
Doses 5 and 6 (weeks 24 and 32)—6 mg/kg IV over one h
Dose 7 and beyond (week 36 and on)—10 mg/kg IV over one h

Lecanemab:

Dosing based on actual body weight: 10 mg/kg once every 2 weeks.

Monitoring

Prior to initiation: ApoE4 status (for ARIA risk assessment). MRI head (FLAIR, T2*, gradient echo (GRE) or susceptibility-weighted images (SWI), and diffusion-weighted images (DWI) sequences) prior to 5th, 7th, and 12th infusion (14th infusion instead of 12th for lecanemab).

During treatment, clinicians and caregivers should closely monitor for signs or symptoms that could suggest ARIA (e.g. headache, confusion, neurological deficits, visual disturbance, seizure etc.)

Pharmacokinetics and interactions

Pharmacokinetics

Aducanumab:

Steady-state concentrations of aducanumab were reached by 16 weeks of repeated dosing at four weekly intervals. Aducanumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulins. The terminal half-life is ~24.8 days.

Lecanemab:

Steady-state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg administered every 2 weeks. Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous immunoglobulins. The terminal half-life is 5 to 7 days.

Interactions

There is a lack of data on specific drug interactions. There may be an increased risk of adverse events with antiplatelet and anticoagulant agents. There may be reduced efficacy of other Fc receptor-binding antibody therapies.

References

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Anticholinergics

Anticholinergics inhibit the action of acetylcholine at nicotinic and muscarinic adrenergic receptors. Within neurology, they are mainly used for their antimuscarinic effect in the treatment of PD tremor, other movement disorders (such as dystonia), and over active bladder (OAB) associated with several neurological conditions such as multiple sclerosis. Many different antimuscarinics are in clinical use. They have variable muscarinic receptor selectivity and the ability to cross the blood–brain barrier. Only the drugs commonly used in the management of movement disorders and OAB syndrome are discussed further.

Anticholinergics were the first pharmacological agents used in the treatment of PD. In modern practice, they are usually used as adjuncts to levodopa, particularly in the treatment of tremor. The most commonly used agents, benztropine, orphenadrine, procyclidine, and trihexyphenidyl, have fewer peripheral effects than other antimuscarinics, however CNS side effects, both neuropsychiatric and cognitive, can limit their use in the elderly. Clinically significant differences in efficacy and tolerability across this drug class, have not been established through clinical trials. An increasing number of antimuscarinics are used in the management of OAB; the commonest antimuscarinics in use for this indication are oxybutynin, solifenacin, and tolterodine, and are mentioned in further detail in later text and compared further in Chapter 20, Uro-neurology. These are first-line medical agents for OAB. They can significantly improve a patient's quality of life and are generally safe and well tolerated. Side effects are often predictable and dose-dependent.

Uses

Licensed uses

In the UK

- *Parkinsonism*:

1. *Benztropine* is not available in the UK.
2. *Orphenadrine* is licensed for the treatment of all forms of parkinsonism, including drug-induced extrapyramidal side effects in individuals aged 18 years and older.
3. *Procyclidine* is licensed for use in the management of all forms of parkinsonism in individuals aged 18 years and older.

In the USA

- *Parkinsonism*:

1. *Benztropine* is licensed for use as an adjunct in the treatment of all forms of parkinsonism in individuals aged 18 years and older.

- *Drug-induced extrapyramidal disorder*:

1. *Benztropine* is used for the control of acute and chronic extrapyramidal symptoms in individuals aged 18 and older. It is not useful and potentially harmful in tardive dyskinesia.

- *Muscle spasm*:

1. *Orphenadrine* is licensed for the treatment of painful musculoskeletal conditions, as an adjunct to rest and physical therapy, in individuals aged 18 years and older.

In the UK/USA

- *Parkinsonism and drug-induced extrapyramidal disorder*:

1. *Procyclidine* is licensed for the management of extrapyramidal symptoms resulting from PD or induced by neuroleptic drugs in individuals aged 18 years and older.

2. *Trihexyphenidyl* is licensed in the treatment of extrapyramidal symptoms resulting from PD or induced by neuroleptic drugs in individuals aged 18 years and older.

Off-label uses

- Dystonia (generalized or as an adjunct to botulinum toxin in focal forms), Essential tremor (ET), and Holmes' tremor.

Mechanism of action

- *PD*: with the loss of inhibitory dopaminergic drive in PD, there is excess excitatory cholinergic activity within the striatum. Anticholinergics in PD and other extrapyramidal movement disorders are thought to rebalance the cholinergic and dopaminergic activity of the striatum, thereby improving extrapyramidal symptoms.
- *OAB*: muscarinic antagonists act through inhibition of types 2 and 3 muscarinic receptors to relax detrusor muscle.

Toxicity and side effects

- *Common—Cardiovascular*: hypotension and tachycardia. *Gastrointestinal*: constipation, decreased gastric motility, dry mouth, nausea, and vomiting. *Dermatological*: rash. *Endocrine*: decreased sweating. *Neurological*: dizziness and memory impairment. *Ophthalmological*: blurred vision, diplopia, dry eyes, and mydriasis. *Psychiatric*: agitation, confusion, euphoria, and hallucinations. *Respiratory*: reduced bronchial secretions. *Urological*: prostatism and urinary retention.
- *Serious—Cardiovascular*: angina. *Ophthalmological*: angle-closure glaucoma.

Contraindications

- *Absolute*: hypersensitivity to drug and closed-angle glaucoma.
- *Relative*: gastrointestinal obstruction, prostatism, tachycardia, and cognitive impairment. May exacerbate tardive dyskinesia and MG. As anticholinergics are metabolized by the liver and excreted in the urine, caution is advised in liver and renal impairment; however, no dose alteration is routinely recommended.

Use in special populations

- *Elderly*: elderly patients are more susceptible to cognitive and psychiatric side effects of anticholinergics which may preclude their use in this group of patients.
- *Pregnancy*: safety in pregnancy has not been studied. There are case reports of the safe use of trihexyphenidyl in pregnancy, but there has been reproductive toxicity in animal studies of antimuscarinics used for OAB; hence the manufacturer advises against use in pregnancy, where possible.
- *Lactation*: excretion into breast milk is not known for most anticholinergics. Use with caution.

Efficacy

- *OAB*: meta-analyses have demonstrated there are no major differences in efficacy between the different agents, and they share a similar side effect profile, which includes effects such as dry mouth and cognitive impairment. Individual variations relate to their muscarinic receptor selectivity, pharmacokinetics, and metabolism. Eighty-five per cent of patients who have failed dosage-escalated monotherapy were shown to benefit from combined high-dosage antimuscarinic medications.
- *PD*: The International Parkinson and Movement Disorder Society (MDS) evidence-based review concluded anticholinergics were 'likely efficacious' as symptomatic monotherapy and as an adjunct to levodopa. In the UK, NICE guidelines suggest anticholinergics should only be used as monotherapy in young-onset PD or in patients with severe tremor, and should not be the first choice outside of these cases due to a lack of evidence for their efficacy and a propensity for neuropsychiatric side effects.

Trihexyphenidyl (benzhexol)

- *Dystonia*: trihexyphenidyl is the only anticholinergic assessed in a double-blind trial (n = 31, 32 years or younger) for the treatment of dystonia (torsion dystonia). Seventy per cent had a clinically significant response, with sustained benefit noted in 42% after a mean follow-up of 2.4 years.
- *Parkinsonism*: there are minimal robust efficacy data for the use of trihexyphenidyl in PD. A 6-month randomized, double-blind study (n = 30) with either levodopa alone or in combination with trihexyphenidyl concluded there was no additional benefit to combination treatment. However, methodological flaws in trial design cast doubt on the validity of this result.

Benztropine

- *Parkinsonism*: there is limited evidence from small trials suggesting benztropine is effective in the management of PD. One randomized, double-blind, placebo-controlled, cross-over study (n = 29) found benztropine used as an adjunct in patients on levodopa significantly improved activities of daily living, rigidity, speed of walking, and movement of upper extremities. A further non-randomized, double-blind, cross-over trial (n = 22) comparing benztropine (mean dose 3 g/day) and clozapine for tremor in PD found both agents to be equally effective, with a 30% reduction in tremor.

Orphenadrine

- *Parkinsonism*: a randomized, double-blind, cross-over study of orphenadrine (titrated to 300 mg/day) vs. placebo (n = 16) found significant benefits in balance, posture, walking, rigidity, household tasks, and total physical signs and disabilities ($p < 0.05$). These were rated on the author's own 4-point scale. No significant improvement in tremor was noted.

Procyclidine

- *Parkinsonism*: there are minimal robust trial data for the efficacy of procyclidine in parkinsonism. A 2-month non-randomized trial that investigated the use of procyclidine as an adjunct to other antiparkinsonian medication in patients with parkinsonism ($n = 70$) showed improvement in tremor (40%), rigidity (53%), akinesia (42%), gait (44%), and sialorrhea (58%).

Dosing and monitoring

Dosing

Trihexyphenidyl (benzhexol)

- *Parkinsonism*: start treatment at 1 mg and increase every 4–7 days by 2 mg until maximal symptomatic relief and tolerability. The total daily dose can be divided over the day (tds to qds) and should be given before or after meals. In PD, a dose of 6–10 mg/day is usually adequate. Post-encephalitic parkinsonism may require up to 15 mg/day. Up to half of patients may initially experience minor side effects that will resolve, as they develop tolerance, although, in some cases, this will preclude continued use or dose escalation.
- *Dystonia and ET*: start at 1 mg daily, and increase by 1 mg every 4–7 days to reach 1 mg tds. Then increase by 1 mg every 4–7 days to reach a usual maintenance dose of 2–4 mg tds. Stop dose escalation if side effects occur, and consider restarting after 1–2 weeks.

Benztropine

- *Parkinsonism*: start treatment at 0.5 mg/day. Increase every 5–6 days by 0.5 mg to achieve maximal symptomatic relief. This can be given once at night or in 2–4 divided doses throughout the day. The usual maintenance dose is 1–2 mg/day. Maximum daily dose is 6 mg. Higher doses are often required for drug-induced extrapyramidal disorders.
- *Acute dystonic reactions*: 1–2 mg IV/IM every 8–12 h. Switch to PO after management of acute reaction and withdraw after 1–2 weeks to assess the need for continued therapy.

Orphenadrine

- *Parkinsonism*: start treatment at 150 mg daily in divided doses. Increase gradually in steps of 50 mg every 2–3 days, according to the response. The usual maintenance dose range is 150–300 mg daily in divided doses. The maximum dose is 400 mg/day.

Procyclidine

- *Parkinsonism*: 2.5 mg tds, increased gradually in steps of 2.5–5 mg daily every 2–3 days, if necessary. Maximum 30 mg/day in 2–4 divided doses (60 mg daily in exceptional circumstances).
- *Acute dystonic reactions*: 5–10 mg IM/IV, usually effective in 5–10 min but may need 30 min for relief.

Monitoring

No routine monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.7.
Interactions See Table 23.8.

Table 23.7 Pharmacokinetics of anticholinergics

	Benztropine	Orphenadrine	Procyclidine	Trihexyphenidyl	Oxybutynin	Solifenacin	Tolterodine
Indication	Extrapyramidal disorders				OAB		
Main routes of administration	PO/IV/IM	PO/IV/IM	PO IM/IV	PO	PO	PO	PO
Oral bioavailability	NA	90%	75%	100%	10%	90%	77%
T_{max}	7 h	2 h	1 h	2–3 h	1 h	1–2 h	1–3 h
Protein binding	NA	95%	100%	NA	93%	98%	96%
Metabolism	Hepatic	Hepatic	Hepatic	NA	Hepatic	Hepatic	Hepatic
Elimination half-life	NA	13–20 h	12 h	NA	2–5 h	45–68 h	2–4 h
Elimination routes	Urine	Urine and bile	Urine	Urine	Urine	Urine and faeces	Urine and faeces

IM, intramuscular; IV, intravenous; NA, information not available; PO, oral.

Table 23.8 Interactions of anticholinergics

Pharmacodynamic interactions

With AChEIs, e.g. donepezil, galantamine, and rivastigmine: may reduce the anticholinergic effects

With other anticholinergics: may increase risk of anticholinergic side effects.

With sublingual tablets, e.g. nitrates: may reduce absorption due to failure to dissolve in dry mouth

With drugs that prolong QT interval, e.g. erythromycin: may prolong QT interval

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Antihistamines

Within neurology, antihistamines are commonly used in the management of vertigo and nausea associated with vestibular disorders. The agents most commonly used for vertigo in the UK are cinnarizine and cyclizine. In the USA, cyclizine, diphenhydramine, and meclizine are favoured. Diphenhydramine is often delivered as a salt conjugated to 8-chlorotheophylline (2:1 stoichiometric ratio) to form dimenhydrinate. Theophylline is a weak stimulant and can be used in combination with dimenhydrinate to counteract sedative side effects.

All antihistamines antagonize the H1 receptor. The majority also have strong anticholinergic effects. These dual actions both contribute to their therapeutic effect and their side effect profile.

Unlike the newer, second-generation antihistamines, the older agents used in the treatment of vertigo cross the blood–brain barrier and interact with histaminergic pathways involved in sleep and alertness. This central action is thought to be important for anti-vertigo efficacy, as the beneficial effects are not routinely seen in the newer peripherally acting agents. Through interaction with the histaminergic sleep and alertness pathways, the centrally acting drugs also have a sedative effect. Patients should be warned of this and advised to avoid the use of heavy machinery while on treatment. In the treatment of vertigo and nausea, the use of these agents is typically restricted to 1–7 days, depending on the extent and duration of symptoms, as there are concerns that the vestibular suppressive effect of these medications may prevent the natural process of vestibular compensation, thereby prolonging symptoms.

Of note, betahistine is a histamine-like agent commonly used in the management of Meniere's disease in Europe. Its dominant actions are H1 receptor agonism and H3 receptor antagonism. It is discussed separately in its own monograph (see Betahistine, p. 528).

Uses

Licensed uses

In the UK

- Vertigo:

1. *Cinnarizine* is licensed for the treatment of vestibular disorders, including vertigo, tinnitus, nystagmus, nausea, and vomiting, in individuals aged 5 years and older.
2. *Cyclizine* is licensed for the treatment of vomiting and attacks of vertigo in disorders of vestibular disturbance in individuals aged 6 years and older.
3. *Dimenhydrinate* is not licensed for use in the UK.
4. *Diphenhydramine* is not licensed for the treatment of vertigo in the UK.
5. *Meclizine* is not licensed for use in the UK.

In the USA

- Vertigo:

1. *Cinnarizine* is not licensed for use in the USA.
2. *Cyclizine* is licensed for the treatment of vertigo associated with motion sickness in individuals aged 6 years and older.
3. *Dimenhydrinate* is licensed for the treatment of nausea, vomiting, and vertigo associated with motion sickness in individuals aged 2 years and older.
4. *Diphenhydramine* is licensed for nausea, vomiting, and vertigo associated with motion sickness in individuals aged over 1 month.
5. *Meclizine* is licensed for the treatment of vertigo associated with diseases affecting the vestibular system in individuals aged 12 years and older.

Off-label uses

- Migraine-associated vertigo and vertigo of vestibular origin.

Mechanism of action

Cinnarizine, cyclizine, diphenhydramine, and meclizine are all H1 receptor antagonists and are believed to reduce the symptoms of vertigo by blocking the effects of histamine on smooth muscle in the hair cells of the vestibular canal, thereby rendering the organs less sensitive. Some of their beneficial effects may also be mediated by central anticholinergic and antihistaminergic activity. Cinnarizine may additionally act as an L-type calcium channel blocker and a pressure-sensitive potassium channel blocker, thereby inhibiting the release of neurotransmitters at synaptic terminals supplying the vestibular organs and minimizing vertigo.

Toxicity and side effects

- *Common—Gastrointestinal*: dry mouth, dyspepsia, nausea, vomiting. *Neurological*: drowsiness and headache. *Ophthalmological*: blurred vision.
- *Serious—Cardiovascular*: arrhythmias, hypotension, and QT prolongation. *Gastrointestinal*: hepatic dysfunction. *Haematological*: agranulocytosis. *Immunological*: anaphylaxis, angio-oedema,

bronchospasm, and lupus-like skin reactions. *Neurological*: cognitive impairment, convulsions, and extrapyramidal effects, including psychomotor impairment. *Ophthalmological*: angle-closure glaucoma. *Urological*: urinary retention.

Contraindications

- *Absolute*: hypersensitivity to the individual antihistamine or its excipients. All antihistamines mentioned in this section should be avoided in porphyria.
- *Relative*: use with caution in patients susceptible to angle-closure glaucoma and in patients who suffer from epilepsy, obstructive disease of the gastrointestinal tract, parkinsonism, prostatic hypertrophy, or urinary retention.

No specific studies have been performed in patients with hepatic and renal dysfunction; hence antihistamines should be used with caution in these groups and avoided in patients with moderate-to-severe hepatic impairment, as they may precipitate coma.

Use in special populations

- *Elderly*: dosing is typically the same as adult doses; however, the elderly are more prone to sedative and anticholinergic side effects.
- *Pregnancy*: animal studies have not shown teratogenicity. However, there have been no controlled studies in humans; hence as a precaution, manufacturers advise avoidance of antihistamines in pregnancy, where possible.
- *Lactation*: for many of the antihistamines, it is not known whether they are excreted into breast milk; hence, as a precaution, the manufacturers advise avoidance, where possible, by nursing mothers.

Efficacy

Evidence for the efficacy of most antihistamines comes from small studies demonstrating good effect in reducing the severity and frequency of vertigo attacks. Rationale for use is based on these studies and expert consensus. There is no conclusive evidence that any one antihistamine is more effective than another in the management of vertigo. There is some evidence that combining two antihistamines, specifically dimenhydrinate and cinnarizine, may be more effective than either agent alone; one randomized clinical trials (RCT) investigating acute unilateral vestibular loss found that combination treatment with 20 mg cinnarizine and 40 mg dimenhydrinate was significantly more effective than either agent alone ($p < 0.001$) after 1 and 4 weeks of treatment. A recent metanalysis, with 7 trials comprising of 802 patients, compared antihistamines to benzodiazepines in the treatment of acute vertigo. This study demonstrated a greater 16.09/100 point greater reduction in visual analogue scale score at 2-h for antihistamines compared to benzodiazepines. There was no significant difference when compared to nonbenzodiazepine interventions at 2-h including piracetam, metoclopramide, droperidol, or ondansetron; however, the authors feel that this may be due to relatively small sample size.

Dosing and monitoring

Dosing

- *Cinnarizine*: 30 mg up to tds.
- *Cyclizine*: 50 mg up to tds.
- *Diphenhydramine*: 25–50 mg every 6 h. Up to 100 mg can be given qds, if required.
- *Dimenhydrinate*: 50–100 mg up to qds. Maximum daily dose is 400 mg.
- *Meclizine*: treatment is 25–100 mg/day in divided doses.

Monitoring

No routine monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.9.
Interactions See Table 23.10.

Table 23.9 Pharmacokinetics of antihistamines

	Cinnarizine	Cyclizine	Diphenhydramine	Meclizine
Main routes of administration	PO	IV/IM/PO/SC	PO/IM/IV	PO
Oral bioavailability	Highly variable	~50%	40–60%	NA
T_{max}	2.5–4 h	2 h	2 h	3 h
Protein binding	91%	NA	98.5%	91–99%
Metabolism	Hepatic: CYP2D6	Hepatic: demethylation	Hepatic: CYP2D6	Hepatic: CYP2D6
Elimination half-life	3–6 h	~14 h	9 h	5–6 h
Elimination	1/3 urine; 2/3 stool	Urine as metabolites	Urine as metabolites	Urine and faeces—exact proportion not known

NA, information not available.

Table 23.10 Interactions of antihistamines

Pharmacodynamic interactions
With alcohol and other CNS depressants: increased risk of sedation
With betahistine and histamine: antagonism (theoretical in the case of betahistine) of effects of these drugs
With monoamine oxidase inhibitors (MAOIs) and TCAs: increased risk of anticholinergic and sedative side effects

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Armodafinil and modafinil

Armodafinil and modafinil are non-amphetamine based stimulant medications, which are licensed for the treatment of excessive sleepiness in sleep disorders such as narcolepsy, shift work sleep disorder, and obstructive sleep apnoea. Modafinil was first approved in 2002 in the UK and 1998 in the USA. Armodafinil was subsequently approved in 2007 by the FDA, but has not received approval in the UK. They are similar compounds. Modafinil consists of a racemic mixture of both stereoisomers, whilst armodafinil solely contains the *R*-enantiomer.

Uses

Licensed uses

In the UK

- *Narcolepsy*: modafinil is licensed for the treatment of excessive sleepiness in the management of narcolepsy, with or without cataplexy, in individuals >18 years of age.

In the USA

- *Narcolepsy/Shift work sleep disorder/obstructive sleep apnoea*: armodafinil and modafinil are licensed for the treatment of excessive sleepiness in these conditions in individuals >18 years of age.

Off-label uses

Treatment of fatigue and hypersomnia related to alpha-synucleioinopathies, Kleine–Levin syndrome, muscular dystrophy, MS, and traumatic brain injury.

Mechanism of action

Modafinil is a racemic mixture of *R*- and *S*-enantiomers, whilst armodafinil is just the *R*-enantiomer. This is the longer-lasting isomer. Hence, the two medications have similar pharmacological properties. Their precise mechanism of action is unclear. Studies have demonstrated that they have a marked wake-promoting action, without an effect on the occurrence of cataplexy. They have been shown to block dopamine and, to a lesser extent, noradrenaline reuptake by binding to dopamine and noradrenaline transporters. Part of their action may also be mediated by elevating hypothalamic histamine levels.

Toxicity and side effects

- *Common—Cardiovascular*: chest pain, palpitations, tachycardia, and vasodilatation. *Gastrointestinal*: abdominal pain, abnormal LFTs,

anorexia, constipation, diarrhoea, dry mouth, dyspepsia, and nausea. *Neurological*: headache is very common (>20%) and dose-dependent, and normally resolves within a few days. Dizziness, fatigue, and paraesthesiae are common. *Ophthalmological*: blurred vision. *Psychiatric*: confusion, insomnia, and mood disorders.
- *Serious—Cardiovascular*: arrhythmia. *Dermatological*: angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome, and toxic epidermal necrolysis are very rare but have been reported. *Immunological*: multiorgan hypersensitivity reaction has been reported. *Psychiatric*: mania, psychosis, and suicidal ideation have been reported.

Contraindications

- *Absolute*: cardiac arrhythmias, history of cor pulmonale, left ventricular hypertrophy, or CNS stimulant-induced mitral valve prolapse, hypersensitivity to armodafinil, modafinil or their excipients, and uncontrolled hypertension.
- *Relative*: presence or history of alcohol or drug abuse, hypertension, mood disorders, and psychosis. The armodafinil and modafinil dose should be halved in severe hepatic impairment. Limited information is available regarding its use in renal impairment. The pharmacokinetics of a single dose of armodafinil and modafinil are not significantly altered in severe renal failure CrCl <20 mL/min, but exposure to modafinil acid, an inactive metabolite is significantly increased. Hence, the manufacturer advises using with caution in patients with severe renal impairment.

Use in special populations

- *Elderly*: the manufacturer advises using half of the usual starting dose in this population. The elderly are more likely to have cardiovascular disease and may be more at risk of cardiac side effects.
- *Pregnancy*: There is limited data about the use of armodafinil and modafinil in pregnancy; however, several case series have identified increased risk of congenital malformations when the foetus has been exposed in the first trimester. The reported anomalies include cardiac defects, skeletal, and urological deformities. The manufacturer advises against use in pregnancy and recommends women of childbearing age take appropriate contraception (oestrogen levels in oestrogen-containing contraceptives are reduced with these medications, hence alternative contraceptives are required).
- *Lactation*: animal studies have demonstrated modafinil secretion in mammalian milk. *R*-modafinil is present in the breastmilk of lactating mothers and small amounts are present in the serum of breastfed infants. No adverse effects have been reported from a small number of case reports. Consider breastfeeding whilst taking these medications if the potential benefits outweigh risks and monitor infants for potential adverse effects.

Efficacy

Armodafinil: One 12-week, multicentre, placebo-controlled, parallel-group, double-blind study of outpatients who met the criteria for narcolepsy showed statistically significant improvement in both sleep latency, as assessed by the maintenance of wakefulness test (MWT) and the change in the patient's overall disease status, as measured by the Clinical Global Impression of change scale (CGI-C). The MWT improved by 2.6 min with the 250 mg dose of armodafinil, compared with a deterioration of 1.9 min with a placebo ($p < 0.01$).

Modafinil: A meta-analysis of 1054 patients with narcolepsy concluded that modafinil led to an improvement in the Epworth Sleepiness Scale; a WMD of −2.73 points (95% CI −3.39 to −2.08), when compared to placebo. The incidence of cataplexy was similar in both the modafinil and placebo groups. Both the American Academy of Sleep Medicine and the European Academy of Neurology established task forces to complete a review of recommendations for the treatment of narcolepsy in 2021. Both concluded that modafinil was recommended as a first-line agent for the treatment of narcolepsy as well as hypersomnia.

Dosing and monitoring

Dosing

Narcolepsy:

Armodafinil: Start treatment at 150 or 250 mg once daily in the morning.

Modafinil: Start treatment at 200 mg daily in 1–2 divided doses. If administered as one dose, give in the morning; if as two doses, administer the second at noon. This can be increased by 100 mg increments to a maximum of 400 mg. The evidence is inconsistent as to whether high doses improve clinical outcomes.

Shift work disorder:

Take 150 mg of armodafinil or 200 mg of modafinil an hour before starting work.

Monitoring

A blood pressure (BP) and an ECG should be recorded at baseline. BP and heart rate should be monitored frequently throughout therapy, and treatment should be discontinued if arrhythmias, chest pain, or uncontrolled hypertension arises.

Pharmacokinetics and interactions

Pharmacokinetics

Modafinil is a racemic mixture of *R*- and *S*-enantiomers. Armodafinil consists solely of the *R*-enantiomer. These enantiomers are similar with respect to their pharmacological activity but differ in that the *R*-enantiomer has a three-times longer half-life than the *S*-enantiomer. The bioavailability of these medications is unknown. Peak plasma levels occur 2–4 h post-dose for both medications. Food co-ingestion does not affect bioavailability; however, it does delay peak plasma levels by 1–4 h. Modafinil is ~60% bound to plasma proteins. These medications are primarily eliminated by hepatic metabolism, including hydrolytic deamination, S-oxidation, etc. The metabolites are pharmacologically inactive. Due to it consisting of a racemic mixture of enantiomers plasma concentrations of modafinil decline in a biphasic manner, compared to armodafinil, where the elimination is monophasic. This means that the exposure to armodafinil was approximately a third greater than with modafinil. Both medications may cause weak induction of

CYP3A4/5 activity, but the effect is felt to be clinically insignificant. They are ultimately eliminated by the renal tract, <10% as unchanged modafinil. The terminal half-life for both armodafinil and modafinil is ~15 h.

Interactions

See Table 23.11.

Table 23.11 Interactions of armodafinil and modafinil

Medications which alter armodafinil and modafinil plasma levels	Medications whose plasma levels are altered by armodafinil and modafinil
Levels decreased: inducers of CYP3A4/5 (e.g. carbamazepine, phenobarbital, rifampin) **Levels increased:** inhibitors of CYP3A4/5 (e.g. ketoconazole, erythromycin)	**Levels decreased:** oestrogen component of contraceptives. *In vitro* testing has suggested there may be induction of CYP3A enzymes, resulting in a reduction in drugs metabolized by this pathway, including ciclosporin, HIV protease inhibitors, and midazolam **Levels increased:** due to possible suppression of CYP2C19 and CYP2C9, the following drug levels may rise: diazepam, omeprazole, phenytoin, propranolol, SSRIs, TCAs, and warfarin

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Atypical antipsychotics

The atypical antipsychotics (risperidone, olanzapine, quetiapine, clozapine, and aripiprazole) are associated with a reduced rate of tardive dyskinesia, compared with their typical predecessors. For this reason, they are now favoured for the treatment of several neurological conditions. Risperidone, olanzapine, and aripiprazole has largely replaced the use of haloperidol and pimozide in the management of tic disorders; quetiapine and clozapine are widely used in the treatment of PD psychosis and olanzapine; risperidone and sulpiride can be used second line in the management of chorea. It is important to remember that the atypical antipsychotics carry a significant risk of metabolic syndrome, as characterized by obesity, insulin resistance, hypertension, and dyslipidaemia, parameters which require regular monitoring and management. Clozapine, although a very effective drug for PD psychosis, is associated with agranulocytosis, which requires registration with a clozapine monitoring service and regular monitoring of full blood count (FBC).

Uses

Licensed uses

In the UK (clozapine is not licensed for the management of PD in the USA)

- *PD*

1. *Clozapine* is licensed for the treatment of psychotic disorders arising in PD where standard therapies have failed in individuals aged 18 years and older.

Off-label uses

1. *Aripiprazole*: tics and TS.
2. *Clozapine*: PD-related psychosis, chorea, and dystonia.
3. *Risperidone*: chorea, tics, and TS.
4. *Quetiapine*: psychosis present in PD and DLB.

Mechanism of action

Their action is primarily through the inhibition of dopaminergic receptors. Compared to typical antipsychotics, they are associated with a reduced incidence of extrapyramidal side effects, which may be the result of their additional affinity for serotonergic receptors. The wider receptor profiles of each agent are highlighted in Table 23.12 and can be used to predict likely side effects.

Toxicity and side effects

- *Common—cardiovascular*: peripheral oedema and tachycardia. *Gastrointestinal*: abdominal pain, appetite increased, constipation, drooling, elevated liver enzymes, nausea, vomiting, and weight gain. *Neurological*: akathisia, anxiety, dizziness, fatigue, headache, insomnia, sedation, and somnolence.
- *Serious—cardiovascular*: arrhythmia, AV block, cardiac arrest, chest pain, and ischaemic heart disease. *Gastrointestinal*: aspiration, hepatic failure, hypercholesterolaemia, intestinal obstruction,

Table 23.12 Relative receptor affinities of atypical antipsychotics

Drug	D1	D2	D3	D4	5HT1	5HT2	5HT2A	α1	α2	ACh	H1
Aripiprazole	+	++++	?	?	++	?	+++	–	–	++	-
Clozapine	+	++	?	+	+	++	+	+++	+++	+++	++
Olanzapine	++	+++	+	+	–	++	++	+++	+	+	+++
Risperidone	+	+++	?	+	+	–	+++	+++	+++	-	+
Quetiapine	+	++	+	–	–	+	+++	+++	+	-	+++

++++, very high; +++, high; ++, moderate; +, low;?, unknown.

Adapted from *CNS Spectrums*, 10(S10), Fernando Cañas, Mechanisms of Action of Atypical Antipsychotics, pp. 5–11, Copyright (2005), with permission from Cambridge University Press.

and pancreatitis; *Haematological*: agranulocytosis and thrombotic thrombocytopenic purpura. *Neurological*: akinesia, NMS, seizures, stroke, and tardive dyskinesia. *Ophthalmological*: angle-closure glaucoma. *Psychiatric*: depression, homicidal ideation, intentional injury.

In addition, with clozapine:

- *Serious—cardiovascular*: cardiomyopathy, myocarditis, and QT prolongation. *Haematological*: agranulocytosis (rare—0.38% in one cohort, not dose-dependent).

Contraindications

- *Absolute*: hypersensitivity to drug or its excipients.
- *Relative*: use with caution in patients with epilepsy, predisposition to long QT syndrome, cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.
    1. *Aripiprazole*: pathological gambling has also been associated with aripiprazole use, so use with caution in patients with a prior history of gambling. No dosage adjustment in renal or mild-to-moderate hepatic impairment. Use with caution in severe impairment.
    2. *Clozapine*: due to anticholinergic effects, caution should be taken with those with prostatic hypertrophy and susceptibility to angle-closure glaucoma. No dosage adjustment in mild-to-moderate renal impairment or mild hepatic impairment.
    3. *Risperidone*: patients with impaired hepatic or renal function should have their doses halved, and up-titration should occur cautiously with minimal increments in doses.
    4. *Quetiapine*: no dose alteration in renal dysfunction. In hepatic impairment, start at a lower dose, due to extensive liver metabolism. Immediate-release: 25 mg daily; increase dose by 25–50 mg daily to effective dose. Extended release: 50 mg od; increase dose by 50 mg/day, as tolerated.

Use in special populations

- *Elderly*: no dosage alteration is routinely recommended; however, the elderly are more prone to orthostatic hypotension, and trials of antipsychotics in elderly patients with dementia have suggested that there is an increased incidence of cerebrovascular events.
- *Pregnancy*: adverse events have been noted in animal studies; however, teratogenicity has not been identified so far in limited human data. Neonates born to mothers taking antipsychotics may exhibit extrapyramidal signs or withdrawal signs. Atypical antipsychotics should only be used in pregnancy if the benefits outweigh the risks.
- *Lactation*: all the atypical antipsychotics mentioned are excreted in breast milk. Limited data suggests that neonates exposed to atypical antipsychotics in breastmilk generally do well. Use if benefits outweigh risks. Infants should be monitored for excessive sedation.

Efficacy

1. *Aripiprazole*: a 10-week multicentre, double-blind, randomized, placebo-controlled trial ($n = 61$) of aripiprazole in children and adolescents with TS found that there was a significant reduction in Yale

Global Tic Severity Scale (YGTSS), compared to placebo (−15.0 vs. −9.6, respectively; p = 0.0196). A further RCT (*n* = 60) comparing aripiprazole with risperidone over 2 months of treatment suggested there was little difference in improvement of YGTSS and health-related quality of life scores between medications, although risperidone was found to improve patient social functioning more than aripiprazole.

2. *Clozapine*: has been shown in several double-blind RCTs to be effective in the treatment of PD psychosis. The first study to demonstrate its effectiveness reported that the Clinical Global Impression score (a score of symptom severity in disorders of mental health) improved by 1.8, compared to 0.6 in the placebo group (p = 0.001). It was well tolerated at 6.25–50 mg/day (doses used in schizophrenia are far higher at 300–800 mg/day). Both this study and a further European RCT have suggested that the symptoms of parkinsonism were not worsened at these doses; in fact, tremors may improve with treatment. The recent MDS review classed it as efficacious and that the associated risks are acceptable so long as treatment is carefully monitored.
3. *Risperidone*: is the best-studied atypical antipsychotic for treatment of tics and TS. Efficacy vs. placebo has been demonstrated in two RCTs of both children and adults with mean daily doses of about 2.5 mg (range 1–6 mg/day). In two randomized, double-blind, cross-over studies, it was at least equally effective and possibly slightly more effective than pimozide. Risperidone may also be beneficial for coexistent aggressive behaviour and obsessive-compulsive symptoms. A survey of expert opinion, published within the European guidelines for treatment of TS, highlights risperidone as the first-line treatment of choice for tics in children and adolescents. However, due to the wider side effect profile of antipsychotics, α2-adrenergic agonists are often used first-line in patients with moderate-severity tics.
4. *Quetiapine*: has been studied in several trials (open-label and double-blind, placebo-controlled trials) with conflicting results. Open-label studies showed it to be ineffective but well tolerated, without motor worsening. Small, low-quality double-blind trials have suggested it may be effective. Expert consensus suggests it is useful in treating PD psychosis when used at low doses; it only carries limited risk of motor worsening, and its side effect profile is significantly better than clozapine, and hence it is often used first-line for this indication.

Dosing and monitoring

Dosing

Aripiprazole: start treatment at 2.5 mg; this can be increased by 1.25–2.5 mg in 1-week intervals, as required/tolerated, to a maximum daily dose of 30 mg. The largest case series to date (*n* = 100) found great variation in maintenance dose, with mean doses of 17.0 ± 9.6 mg/24 h.

Clozapine: start treatment at 6.25–12.5 mg at night, and increase by 12.5 mg no more than twice a week. The minimal effective dose is usually 25–37.5 mg/day. The maximum recommended dose is 50 mg/day, although rarely doses of 100 mg/day in 1–2 divided doses have been used. Once maintenance dose is reached, this should be maintained for 2 weeks before PD medications are altered.

If stopping for a reason other than a serious or life-threatening side effect, the dose should be tapered over 1–2 weeks, with 12.5 mg interval reductions. Monitor for rebound psychosis.

Risperidone: start treatment at 0.25 mg od for 2 days, then increase to 0.5 mg/day in two divided doses for 3 days, then 1 g/day in two divided doses for 3 days. Thereafter, increase in increments of 0.5 mg/day every 3–4 days, as required/tolerated, up to a usual maintenance dose of 2.5 mg/day. The maximum dose used in trials was 6 mg/day.

Quetiapine: start treatment at 12.5–25 mg at night. Increase every 1–2 days, until symptoms improve. The usual effective dose is 75–200 mg in 2–3 divided doses. The maximum dose is 200 mg/day.

Monitoring

Monitor body mass index (BMI), BP, FBC, glucose, and thyroid, renal, and liver function, as well as lipid panels, on a regular basis.

Clozapine monitoring: all patients should be registered with a clozapine monitoring service. An FBC should be taken at baseline, then weekly for 18 weeks, and monthly thereafter, in view of the risk of agranulocytosis. Stop the drug if absolute neutrophil count is <1.5 × 10^9/L or white cell count (WCC) <3.0 × 10^9/L.

Patients should be advised that, if they experience flu-like symptoms, a rash, or a fever, which may indicate a low WCC or agranulocytosis, they should stop the drug and seek urgent medical advice.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.13
Interactions See Table 23.14

Table 23.13 Pharmacokinetics of atypical antipsychotics

	Aripiprazole	Clozapine	Quetiapine	Risperidone
Main routes of administration	PO	PO	PO	PO
Oral bioavailability	87%	60–70%	9%	70%
T_{max}	1–3 h	2.5 h	1.5 h	1 h
Protein binding	99%	95%	83%	90%
Metabolism	Hepatic CYP2D6, CYP3A4	Hepatic CYP1A2, CYP3A4	Hepatic CYP3A4	Hepatic CYP2D6, CYP3A4
Pharmacologically active metabolites	Yes, dehydro-aripiprazole	Yes, norclozapine	Yes, *N*-desalkyl-quetiapine	Yes, 9-hydroxy-risperidone
Elimination half-life	75 h	8–12 h	3 h	3 h
Excretion	Urine (27%), faeces (60%)	Urine (50%), faeces (30%)	Urine (73%), faeces (21%)	Urine (70%), faeces (14%)

PO, oral.

Table 23.14 Interactions of atypical antipsychotics

Medications which alter atypical antipsychotic plasma levels	Pharmacodynamic interactions
Levels increased: CYP3A4, CYP2D6, and CYP1A2 inhibitors. **Levels decreased**: CYP3A4, CYP2D6, and CYP1A2 inducers. (dependent on method of metabolism; see pharmacokinetics,Table 23.13)	**With CNS depressants, e.g. alcohol**: enhanced sedative effects **With agents known to prolong QTc, e.g. chlorpromazine and macrolide antibiotics**: increased risk of ventricular arrythmia **With other antipsychotics (e.g. sulpiride)**: may increase the risk of antipsychotic toxicity **With tetrabenazine**: increased risk of extrapyramidal side effects

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Benzodiazepines

Chlordiazepoxide was the first benzodiazepine to be synthesized, in 1955, shortly followed by diazepam in 1963. Benzodiazepines are used for a wide range of indications within neurology, including epilepsy, insomnia, and other sleep disorders, spasticity, and movement disorders. While they are highly effective drugs for the majority of these indications, the drawbacks of all benzodiazepines include the risk of rebound seizures if withdrawn too rapidly, sedative side effects, and potential for abuse.

For epilepsy, there are two main groups of benzodiazepines. The first group, comprising diazepam, lorazepam, and midazolam, is primarily used in the early management of status epilepticus. They are highly effective and have a rapid onset of action, with multiple routes of administration. The second group includes clobazam and clonazepam, drugs more commonly used in the longer-term management of chronic epilepsy, typically as an adjunct when first- and second-line treatments have failed. They are useful against a wide range of seizure types and can result in dramatic seizure reduction in refractory cases, or, in the case of clobazam, when used short-term, to manage acute flares of seizure activity. However, a large proportion of patients will develop tolerance if these medications are used in the medium to long term. Temazepam is the final benzodiazepine to be discussed in this book; unlike the aforementioned drugs, it has not found a use in epilepsy, but rather it is used for its sedative effects in the short-term management of insomnia.

Uses

Licensed uses

In the UK

- Epilepsy:
    1. *Clobazam* is licensed for the treatment of non-convulsive status epilepticus and as intermittent adjunctive therapy in the treatment of partial or generalized seizures in individuals over three years old.
    2. *Clonazepam* is licensed for the treatment of generalized seizures, including absence, clonic, myoclonic, tonic, and tonic–clonic types. It is also licensed for the treatment of focal-onset seizures with or without secondary generalization. As an IV infusion, it is licensed in the treatment of status epilepticus. All of its licences are for individuals of all ages.
    3. *Diazepam*: the oral/rectal form is licensed for the treatment of epileptic and febrile convulsions. The oral form is licensed as an adjunct in certain types of epilepsy, e.g. myoclonus. The IV form is licensed for the treatment of status epilepticus and febrile convulsions.
    4. *Lorazepam* is licensed for the treatment of status epilepticus in its IV form in individuals of all ages.
    5. *Midazolam*: the oromucosal form is licensed for the treatment of prolonged, acute, convulsive seizures in individuals aged from 3 months to <18 years of age.

In the USA

- Epilepsy:
    1. *Clobazam* is licensed for adjunctive therapy of Lennox–Gastaut syndrome (LGS) in patients 2 years or older;
    2. *Clonazepam* is licensed for the treatment of akinetic, absence, and myoclonic seizures, as well as LGS, in individuals of all ages;
    3. *Diazepam*: the rectal form is licensed for the treatment of refractory epilepsy as an intermittent therapy to control bouts of increased seizure frequency. The oral form is licensed for use as an adjunct in the treatment of convulsive disorders and as an adjunct for muscle

   spasms, spasticity, athetosis, and stiff-man syndrome. The IV form is licensed for use in status epilepticus.
4. *Lorazepam* is licensed for the treatment of status epilepticus in its IV form in individuals of all ages.
5. *Midazolam* is not licensed for the treatment of epilepsy in the USA.

Off-label uses

1. *Clobazam* is used in the management of catamenial epilepsy and withdrawal epilepsy.
2. *Clonazepam* is used in the management of ET, myoclonus (both cortical and subcortical), nocturnal spasm, parasomnias (non-rapid eye movement (REM) and RBD), restless legs syndrome (RLS), short-term relief of spasticity, and tic disorders.
3. *Lorazepam* is used in the management of myoclonic seizures.
4. *Midazolam* can be used as intermittent therapy to control acute repetitive seizures and for the control of status epilepticus in adults.

Mechanism of action

The benzodiazepines all share certain pharmacological properties. As a group, they bind to ionotropic GABA-A ligand-gated chloride channel complexes, potentiating the action of GABA by increasing transmembrane chloride conductance. The resulting post-synaptic hyperpolarization inhibits the propagation of action potentials.

Certain benzodiazepine agents are used preferentially in epilepsy, and others as anxiolytics or hypnotics, for two primary reasons:

1. Differences in pharmacokinetic profile (determined, in large part, by the varying degree to which a benzodiazepine is lipid-soluble).
2. Individual benzodiazepines have varying activity at different GABA-A receptor subunits. GABA-A channels are synthesized from several different subunits, which are uniquely distributed throughout the nervous system, and these individual subunits have different clinical impacts. For example, the α-1-GABA-A subunit mediates anticonvulsant activity and some sedative side effects of benzodiazepine treatment, while the α-2-GABA-A subunit is important in anxiolysis.

Toxicity and side effects

- *Common—Gastrointestinal*: anorexia, constipation, and dry mouth. *Neurological*: fatigue and drowsiness are common and can sometimes be severe—this is often minimized by smaller doses and giving the medication at night. Ataxia and confusion can occur, particularly in the elderly. *Psychiatric*: behavioural disturbances are also relatively common—aggression, depression, insomnia, and hyperactivity can occur, particularly in the elderly.

- *Serious—Cardiovascular*: acute IV administration may result in hypotension. *Haematological*: blood dyscrasias have rarely been reported. *Neurological*: withdrawal syndrome following chronic use, including rebound seizures, if suddenly stopped. *Psychiatric*: dependence, tolerance, and withdrawal phenomena. *Respiratory*: rarely respiratory depression and apnoea can occur.

Contraindications

- *Absolute*: individuals with a risk of respiratory depression, including acute pulmonary disease, obstructive sleep apnoea, marked respiratory muscle weakness, and pre-existing respiratory depression. They are also contraindicated in severe hepatic impairment.
- *Relative*: pre-existing mood disorders, e.g. chronic psychosis, depression, and obsessional/phobic disorders. A history of drug or alcohol abuse and in those with muscular weakness, including MG. Alcohol and opioids, among other drugs, should be avoided. Smaller doses are recommended in patients with renal impairment, as benzodiazepines are renally excreted, and these individuals tend to be more sensitive to side effects. Reduce the dose in mild-to-moderate hepatic impairment.

Use in special populations

- *Elderly*: the elderly population have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens. Polypharmacy is also more likely in the elderly, and hence the risk of pharmacokinetic interactions is high.
- *Pregnancy*: human studies have demonstrated teratogenic potential for many of the benzodiazepines, especially during the first and last trimesters. Neonates are at risk of flaccidity and withdrawal, with symptoms such as hypothermia, respiratory depression, etc. Use in pregnancy involves weighing up the potential benefits and side effects (see Antiepileptic drugs in young women, p. 38).
- *Lactation*: all the benzodiazepines are present, to varying extent, in mammalian breast milk. If used by nursing mothers, infants should be monitored for potential side effects such as drowsiness and poor interaction. They should be switched to alternative methods of feeding if these are identified.

Efficacy

1. *Clobazam*: several RCTs have shown a 50% or greater reduction in seizure frequency, compared to placebo, in 52–57% of patients treated for refractory partial epilepsy. A 2008 Cochrane review concluded that it may have most benefit in focal-onset seizures. One large Canadian retrospective study found that, in up to 50% of patients, clobazam can be used for 4 years or more prior to the development of clinically significant tolerance.
2. *Clonazepam*: evidence for the use of clonazepam for any of its neurological indications are typically based on observational studies, and there is little concrete evidence of efficacy in the form of RCTs. Many case series and trials have noted high levels of dropout due to side effects, predominantly ataxia, confusion, and sedation.

- *Epilepsy*: clonazepam is thought to be particularly effective in the management of myoclonic seizures.
- *ET*: evidence is conflicting, with some studies suggesting no effect and others minimal improvement in tremor.
- *Myoclonus*: strong conclusions cannot be drawn from studies; however, expert opinion suggests clonazepam is probably effective.
- *Parasomnias*: the best practice guide for management of RBD (2010) identified from 22 studies (predominantly case series) that 306 out of 339 patients had a complete or partial response to treatment. There is less evidence for use in non-REM parasomnias, although some case series of patients with injurious sleep-walking and sleep terrors showed that patients could have a sustained response to clonazepam over a mean period of 3.5 years.
- *RLS*: clonazepam improves sleep quality but does not have an effect on the core clinical symptoms of RLS. One small RCT (*n* = 6) found significant improvement in RLS-related sleep efficiency (89% vs. 73% with placebo) with 1 mg of clonazepam.

3. *Spasticity*: small observational studies from the 1970s and 1990s suggest a beneficial clinical and electrophysiological effect in patients with spasticity associated with cerebral palsy and MS.3. *Diazepam/lorazepam*: see Status epilepticus, p. 43.
4. *Midazolam*: for status epilepticus, evidence for use of midazolam is predominantly extrapolated from children to the adult population. A large meta-analysis of children and young adults (*n* = 774) established that buccal midazolam was both more effective at terminating seizures than rectal diazepam (RR 1.54, 95% CI 1.29–1.85) and could be administered faster (mean difference in time to administration 2.46 min).

Dosing and monitoring

Dosing

1. *Clobazam*: for the treatment of epilepsy, age >12 years—start treatment at 5–10 mg/day at night. This can be increased by 5 mg/day in weekly intervals. The normal maintenance dose is 20–30 mg/day, as either one dose at night or two divided doses with the larger dose at night. The recommended maximum dose is 60 mg/day.
2. Clonazepam:
    - *Epilepsy*: 1 mg at night for 4 days. This can be increased over 2–4 weeks to a maintenance dose of 4–8 mg. Doses of >4 mg/day require bd dosing;
    - *ET/myoclonus/nocturnal spasms/spasticity*: start treatment at 0.5 mg at bedtime. Doses can be increased cautiously in 0.5 mg increments every 3–4 days to a maximum of 6 mg for ET and 4 mg for nocturnal spasms. If used as an adjunctive therapy in the treatment of spasticity or in the management of myoclonus, much higher doses of 20 mg/day and 15 mg/day in 3–4 divided doses have been used in case series (few patients are able to tolerate doses this high);
    - *Status epilepticus* (IV): 1 mg given over 2 min into a large vein. This can be repeated up to three times in 3 h;

- *Parasomnia*: recommended doses are between 0.25 mg and 2 mg at night prior to sleep. This has been increased to 3 mg in case studies of non-REM parasomnia and 4 mg in case studies of RBD;
- *RLS*: 0.5–1 mg at bedtime is the typical dose.

3. *Diazepam*: within the context of epilepsy, diazepam is predominantly used for status epilepticus where the need for rapid administration is paramount. Oral dosing would mean that maximum plasma levels are attained between 30 and 90 min post-dose. Rectal solution (gels are slower) reaches maximum plasma concentration at 10–60 min. Hence, IV injection is the first line in status epilepticus, and rectal administration is used only if IV access is unavailable.
    - IV injection in status epilepticus, age >12 years: 10–20 mg (5 mg/mL) given over 1 min, and repeated once after 10 min, as necessary. Maximum dose of 3 mg/kg body weight over 24 h.
    - Rectal administration as solution in status epilepticus, age >12 years: 10–20 mg; repeat once after 10 min, as required. Doses limited to 10 mg are recommended for the elderly.
4. *Lorazepam*: IV injection in the treatment of status epilepticus, age >12 years—4 mg by slow IV infusion, not exceeding 2 mg/min. This can be repeated once after 10 min, if required. This should be into a large vein to minimize local irritation and thrombophlebitis. In ongoing status, PO or IV maintenance at 4 mg, tds to qds, can be continued.
5. *Midazolam*: buccal administration for emergent status epilepticus, age >18 years.

Therapeutic drug monitoring (rarely required with benzodiazepines)

1. *Clobazam*: optimum seizure control occurs at plasma clobazam levels of 0.03–0.30 mg/L and *N*-desmethylclobazam levels of 0.3–3.0 mg/L.
2. *Clonazepam*: optimum seizure control when used in monotherapy occurs at plasma concentrations of 0.013–0.070 mg/L.
3. *Diazepam*: therapeutic drug monitoring is rarely necessary. Diazepam is primarily intended for use in epilepsy acutely, and not as maintenance therapy. For initial seizure control, plasma levels of ~550 ng/mL are recommended.
4. *Lorazepam*: therapeutic drug monitoring is rarely necessary. Lorazepam is primarily intended for use in epilepsy acutely, and not as maintenance therapy. If used as maintenance therapy, optimum seizure control when used as monotherapy occurs at plasma concentrations of 20–30 micrograms/L.
5. *Midazolam*: therapeutic drug monitoring is rarely necessary. Midazolam is primarily intended for use in epilepsy acutely, and not as a maintenance therapy.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.15.

Interactions See Table 23.16.

As a rule, the benzodiazepines used in epilepsy undergo extensive hepatic metabolism, are eliminated by the renal tract, and do not display autoinduction of liver enzymes.

Table 23.15 Pharmacokinetics of benzodiazepines

	Clobazam	Clonazepam	Diazepam	Lorazepam	Midazolam	Temazepam
Main routes of administration	PO	IV/PO	IV/PO/PR	IV/PO	Buccal/IV/PO	PO
Oral bioavailability	>95%	>80%	~100%	>90%	75% buccal, <50% oral	~100%
T_{max}	1–3 h	1–4 h	30–90 min PO, 10–60 min PR	1.5–2 h	0.5–1 h PO, 25 min buccal	1 h
Protein binding	85%	86%	97–99%	90%	96–98%	75–95%
Time to steady state	2–7 days	2–10 days	6–11 days	~3 days	NA	3 days
Distribution half-life	NA	30 min	2–13 min	<11 min	4–19 min	1–2 h
Pharmacologically active metabolites	Yes, strong	No	Yes, strong	No	Yes, weak	No
Elimination half-life	10–30 h	17–56 h	28–54 h[*]	8–24 h	1.5–4 h	3.5–18 h

[*] Plasma concentrations reduce rapidly initially, with a plasma half-life of ~1 h, due to redistribution into adipose tissue.

IV, intravenous; NA, information not available; PO, oral; PR, per rectum.

Table 23.16 Interactions of benzodiazepines

Medications which alter benzodiazepine plasma levels	Medications whose plasma levels are altered by benzodiazepines	Pharmacodynamic interactions
Levels decreased: cytochrome P450 inducers, e.g. carbamazepine, cimetidine, phenobarbital, and primidone. Oestrogens and progestogens may also reduce temazepam plasma concentrations. **Levels increased:** cytochrome P450 inhibitors, e.g. felbamate, ritonavir, and stiripentol	**Levels increased:** the benzodiazepines may increase plasma levels of carbamazepine, phenytoin, primidone, stiripentol, and valproate	**With CNS depressants, e.g. alcohol, antihistamines, antipsychotics, opioids, and TCAs:** increased sedative effects **With antihypertensives, e.g. ACE inhibitors, α-blockers, etc.:** enhanced hypotensive effects. **With levodopa:** levodopa effects may be antagonized

Diazepam is rapidly and extensively metabolized in the liver to several pharmacologically active metabolites: *N*-desmethyldiazepam, oxazepam, and temazepam. Of these, *N*-desmethyldiazepam can accumulate to levels far in excess of diazepam and contributes much to the anticonvulsant action of diazepam. Diazepam is circulated around the entero-hepatic system, and, as a result, plasma levels can rise again 6–8 h post-dose, as the diazepam is reabsorbed.

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Brivaracetam and levetiracetam

Levetiracetam was first marketed in the US and UK as a broad-spectrum anti-seizure medication (ASM) in 1999 and 2000, respectively. Brivaracetam is a newer racetam drug that was discovered as an analogue of levetiracetam. Both ASMs have simple pharmacokinetics and relatively good side effect profiles. They are widely used in the management of both focal onset and generalized seizures. Brivaracetam may have a superior neuropsychiatric side effect profile when compared to levetiracetam, based on descriptive, non-randomized studies. There are, unfortunately, no head-to-head comparator studies. Levetiracetam is also becoming increasingly used in the treatment of status epilepticus (see p. 357 for further details).

Uses

Licensed uses

In the UK

- *Epilepsy*: Both brivaracetam and levetiracetam are licensed as adjuncts in the treatment of focal-onset seizures with or without secondary generalization in individuals aged 1 month and older.

Levetiracetam is licensed as a monotherapy for the treatment of focal-onset seizures with or without secondary generalization in individuals aged 16 years and older. For individuals older than 12, it is also licensed as an adjunct in the treatment of myoclonic seizures associated with juvenile myoclonic epilepsy, and primary generalized tonic–clonic seizures associated with idiopathic generalized epilepsy.

In the USA

- *Epilepsy*: Both brivaracetam and levetiracetam are licensed for the treatment of focal-onset seizures in patients 1 month of age or older. Levetiracetam is approved as an adjuvant treatment in the treatment of myoclonic seizures in patients older than 12 with juvenile myoclonic epilepsy. It is also approved as an adjunctive therapy in the treatment of generalized tonic–clonic seizures associated with idiopathic generalized epilepsy in individuals aged 6 years and older.

Off-label uses

- Absence and myoclonic seizures, ET, and status epilepticus.

Mechanism of action

The exact mechanism of action of the racetam drugs remains unclear. *In vitro* studies have demonstrated multiple possible mechanisms: some of their effects may be mediated by their binding to synaptic vesicle protein 2A—a protein important for the process of neurotransmitter release.

Toxicity and side effects

- *Common—Dermatological*: rash. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, dyspepsia, nausea, and vomiting. *Neurological*: fatigue and headache are very common. Ataxia, dizziness, seizures, and tremor can occur. *Psychiatric*: aggression, anxiety, depression, and insomnia. *Respiratory*: cough and nasopharyngitis.
- *Serious—Dermatological*: Angioedema, Stevens–Johnson syndrome, and toxic epidermal necrolysis have rarely been reported with levetiracetam. *Gastrointestinal*: hepatic failure and pancreatitis have been reported with levetiracetam. *Haematological*: rarely, pancytopenia can occur. *Psychiatric*: psychotic disorders and suicidal ideation have been reported.

Contraindications

- *Absolute*: hypersensitivity to the drug or its excipients.
- Relative:

Brivaracetam: No dose adjustments are required in renal impairment although the manufacturer advises against use in end-stage renal failure, on dialysis. In the context of hepatic impairment a 50 mg/day starting dose should be considered. A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment.

Levetiracetam: Levetiracetam is predominantly cleared by the renal system; hence dosage needs to be adjusted, depending on the eGFR. For those with normal kidney function (eGFR >80 mL/min/1.73 m^2) the recommended dose is 500–1500 mg bd, with a recommended maximum of 3 g/day. If the eGFR is between 50 and 79 mL/min/1.73 m^2, the recommended dose is 500–1000 mg bd, with a maximum of 2 g/day. If the eGFR is between 30 and 49 mL/min/1.73 m^2, the recommended dose is 250–750 mg bd, with a maximum of 1.5 g/day. If the eGFR is <30 mL/min/1.73 m^2, the recommended dose is 250–500 mg bd, with a maximum of 1 g/day. Patients in end-stage renal failure undergoing dialysis should receive 500–1000 mg once daily with a 250–500 mg supplemental dose following dialysis. The dose should be halved if there is severe hepatic impairment with an eGFR <60 mL/min/1.73 m^2. No dosage changes are required in mild-to-moderate hepatic impairment.

Use in special populations

- *Elderly*: both anti-seizure medications (ASMs) are useful drugs in the elderly, due to the low level of drug interactions and adverse events. A smaller dosage may be required because of age-related renal impairment.
- Pregnancy:

Brivaracetam: There are no adequate data on the developmental risks associated with use of brivaracetam in pregnant women. In animal studies, brivaracetam produced evidence of developmental toxicity at maternal plasma exposures greater than clinical exposures. No information is available on pharmacokinetic changes of brivaracetam during pregnancy. Use in pregnancy involves weighing up the potential benefits and risks.

Levetiracetam: animal studies have demonstrated some teratogenic side effects. Pregnancy registries now include several thousand infants exposed to levetiracetam *in utero* and these have not shown any increase in the levels of congenital malformations. The plasma concentrations of levetiracetam can decrease by up to 60%; hence, an increase in dose may be required. Use in pregnancy involves weighing up the potential benefits and side effects.

- *Lactation*: Limited data suggests that use of brivaracetam during breastfeeding indicates that infants might have serum levels in the therapeutic range with exclusive breastfeeding, but undetectable levels with partial breastfeeding. Until more data are available, brivaracetam should only be used with careful monitoring during breastfeeding. Levetiracetam enters maternal milk, and plasma levels in breastfed infants are <20% of maternal plasma levels. Monitor infants for potential side effects, such as fatigue and irritability, and switch to an alternative feeding regimen if these are identified.

Efficacy

- *Brivaracetam:*
- In a population of adults with uncontrolled focal-onset epilepsy on one or two anti-seizure medications a randomized double-blind placebo-controlled trial showed a statistically significant 50% or more reduction in seizure frequency of 38.9% for brivaracetam 100 mg/day and 37.8% for brivaracetam 200 mg/day against 21.6% for placebo.
- *Levetiracetam:*
- *Monotherapy for general focal-onset seizures, age >16 years:* A 2007 randomized double-blind trial compared the efficacy of 500 mg bd levetiracetam to 200 mg bd extended-release carbamazepine in patients with newly diagnosed partial or generalized tonic–clonic seizures. Over the trial period, incident seizures prompted a dose escalation of up to 1500 mg bd for levetiracetam and 600 mg bd carbamazepine. A comparable number of patients were seizure-free at 6 months (73% vs. 72.8%) in the levetiracetam arm vs. the carbamazepine arm. Adverse event withdrawal rates were comparable in each group (14.4% vs. 19.2%).
- *Adjunctive therapy for focal-onset seizures*: Three multicentre randomized double-blind placebo-controlled studies demonstrated the efficacy of levetiracetam in the treatment of focal-onset seizures in adults. Over the three studies, a total of 904 patients were randomized to one of three levetiracetam doses (1000 mg/day, 2000 mg/day, and 3000 mg/day), or placebo as an adjuvant to their existing ASM routine. All enrolled patients had a history of refractory focal-onset seizures for >1 year with exposure to at least 1 other ASM. For the two studies that used a dose of 1000 mg/day, the dose was found to reduce the mean number of weekly seizures by 26.1% and 17.1% compared to placebo. For the one study that examined a dose of 2000 mg/day, there was a 21.4% reduction in weekly focal-onset seizures. The two studies that examined a dose of 3000 mg bd demonstrated a reduction of 30.1% and 39.4%, respectively.
- *Adjunctive therapy in patients with juvenile myoclonic epilepsy:* A 2008 single-centre, randomized, double-blind, placebo-controlled study of 120 patients >12 years old with juvenile myoclonic epilepsy demonstrated the efficacy of levetiracetam as an adjuvant in this population. For those in the active arm, the dose was titrated up to 1500 mg bd. The primary outcome measured was >50% reduction in myoclonic seizure days per week. A total of 60.4% of those in the active arm had a >50% reduction in seizure days per week compared to 23.7% in the placebo arm.
- *Adjuvant therapy in generalized tonic–clonic seizures:* A 2007 single-centre, double-blind, randomized control study demonstrated the efficacy of levetiracetam as an adjuvant therapy in the treatment of generalized tonic–clonic seizures. Enrolled patients were on a stable dose of 1–2 other ASMs with >3 weekly generalized tonic–clonic seizures at baseline. Patients were treated with 1500 mg bd for 20 weeks. For the active arm, there was a 77.6% reduction in weekly seizures compared to 44.6% in the placebo arm.

For a discussion of the evidence for the use of levetiracetam in status epilepticus, see Chapter 3, Epilepsy.

Dosing and monitoring

Dosing

Brivaracetam

- *Adults/ Children weight greater than 50 kg:* The recommended starting dose is either 50 mg/day or 100 mg/day based on assessment of required seizure reduction versus potential side effects. The dose should be administered in two equally divided doses, once in the morning and once in the evening. The dose may be adjusted in the dose range of 50 mg/day up to 200 mg/day maximum.

Levetiracetam

- *Monotherapy of focal-onset seizures*, age >16 years: start treatment at 250 mg od. This should be increased at 1–2 weeks to 250 mg bd, and then further increased by doses of 250 mg bd in 2-week intervals to a maintenance dose of 1–3 g/day in divided doses.
- *Adjunctive therapy of focal-onset seizures, and myoclonic and tonic–clonic seizures*, age >18 years and >50 kg body weight: start treatment at 250 mg bd and increase by 500 mg bd every 2–4 weeks to a maximum of 3 g/day in divided doses.

Monitoring

Hepatic and renal function should be checked prior to starting treatment. Patients should be monitored for signs of depression and behavioural disturbance.

Therapeutic drug monitoring

Brivaracetam: The current reference range for brivaracetam in plasma is 0.22.0 mg/L.

Levetiracetam: Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 12–46 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Brivaracetam: Oral bioavailability is almost 100%. T_{max} is 0.25–3 h. High-fat meals can increase T_{max} by around 3 h. Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of distribution is 0.5 L/kg. Brivaracetam is rapidly and evenly distributed in most tissues. Brivaracetam undergoes hepatic metabolism mediated primarily by CYP2C19, thus patients who are CYP2C19 poor metabolizer and those using inhibitors of CYP2C19 may require dose reduction. None of the metabolites of the drug are pharmacologically active. ~95% of drugs and metabolites are excreted by the renal system 72 h after intake, and less than 1% is excreted in faeces. Approximately 10% of the dose is excreted without undergoing metabolism. The half-life is ~9 h.

Levetiracetam: Oral bioavailability is almost 100% and is not affected by food co-ingestion. T_{max} is <2 h. Steady state is achieved in 2 days. The compound demonstrates linear pharmacokinetics with <10% protein binding.

Levetiracetam does not undergo significant metabolism. Hydrolysis of the acetamide group, resulting in an inactive metabolite, through a cyp450-independent enzymatic reaction represents the major metabolite. There is no autoinduction. Almost 100% of levetiracetam is eliminated by the kidneys, about two-thirds as the unchanged drug. The half-life is 6–8 h in adults; this is increased to 10–11 h in the elderly. The half-life is directly proportionate to renal CrCl.

Interactions

See Table 23.17.

Table 23.17 Interactions of brivaracetam and levetiracetam

Medications which alter racetam drug plasma levels	Medications whose plasma levels are altered by racetam drugs	Pharmacodynamic interactions
Levels decreased: Both:carbamazepine, phenobarbital, and phenytoin. Brivaracaetam alone: Rifampacin and S Johns Wort. Levetiracetam alone: lamotrigine and oxcarbazepine.	**Brivaracetam alone: Levels increased:** carbamazepine-epoxide metabolite	**Levetircetam alone:** **With carbamazepine, valproate, and topiramate:** may increase the likelihood of side effects. **With CNS depressants, e.g. alcohol and MAOIs:** can enhance sedative side effects

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Cannabinoids

Cannabinoids refer to a group of medications that act on the endocannabinoid system. They are either synthesized artificially or derived from *Cannabis sativa* leaves and flowers. There are a number of different licensed cannabinoid formulations, including medications that have been licensed for the management of anorexia nervosa. There are only two cannibinoids that are currently licensed for neurological indications: Sativex® and Epidiolex®, which are licensed for spasticity and specific forms of epilepsy respectively. Only these two medications will be discussed further. They differ from cannabis and cannabidiol (CBD) oils available both illegally and commercially in their purity and composition. Although a number of active compounds have been identified in the *Cannabis sativa* plants, two main components: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are thought to be responsible for most of cannabis' therapeutic actions. Sativex® is 50% THC and 50% CBD whilst Epidiolex® is 99% CBD. Sativex® was first approved for use in the UK in 2010 as an adjuvant treatment for moderate-to-severe MS-associated spasticity, it is not approved for use in the USA. Epidiolex® was first approved by the FDA in 2018. It was subsequently approved for use in the UK in 2019. It is licensed as an adjunct in the treatment of rare forms of epilepsy, Dravet's syndrome, Lennox–Gastuat syndrome and more recently epilepsy associated with tuberous sclerosis complex.

Uses

Licensed uses

In the UK/USA

- *Epilepsy:* Epidiolex® is licensed for the treatment of seizures associated with Lennox–Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex in patients aged 2 years and older (UK), 1 year and older (USA)

In the UK only

- *Spasticity*: cannabinoids are licensed as an adjunctive treatment for moderate-to-severe spasticity in individuals 18 years and older with MS who have not responded adequately to other anti-spasticity therapies and demonstrate clinically significant improvement during an initial trial of therapy. Sativex® is intended to be used in combination with previously prescribed anti-spasticity medications.

Cannabinoid combinations containing THC are not currently licensed in the USA.

Off-label uses

- Neuropathic pain in MS.

Presentation

- *Trade names*: Epidiolex®, Nabiximols® and Sativex®. Generics are not available.
- *Formulations*: Epidiolex® is available as an oral solution of 100 mL (100 mg/mL). Sativex® is available as an oromucosal spray in 5.5 and 10 mL vials. This delivers 0.1 mL per actuation. Each 0.1 mL spray provides a dose of 2.7 mg THC and 2.5 mg CBD.

Mechanism of action

THC mimics the action of endogenous cannabinoids (endocannabinoids), which are released post-synaptically and act upon presynaptic CB_1 cannabinoid receptors. CB_1 receptors are found throughout the CNS, and peripheral nervous system (PNS)—activation leads to decreased excitability and inhibition of neurotransmitter release at the presynaptic neuron. The resultant changes in synaptic transmission lead to downstream muscle relaxation and improvement of spasticity. In contrast, CBD has a negligible direct agonist effect upon CB_1 receptors. Its postulated effects are wide-ranging and its exact mechanism of action in both epilepsy and spasticity are unknown; however, most of its action is thought to be due to its role as an indirect allosteric antagonist of cannabinoid receptors and as a 5-HT1A receptor agonist. CBD may also modulate the absorption of THC and decrease its breakdown into psychoactive metabolites, thus reducing undesirable psychotropic side effects. In combination, these compounds modulate the endocannabinoid system, which has roles in pain sensation, motor learning, and synaptic plasticity.

Toxicity and side effects

- *Common—cardiovascular*: hypotension, palpitations, tachycardia. *Gastrointestinal*: abdominal pain, anorexia, constipation, diarrhoea, glossodynia, hunger, LFT abnormalities, oral candidiasis, stomatitis, taste disturbance, tooth discoloration, xerostomia. *Musculoskeletal*: weakness. *Neurological*: amnesia, attention deficit, confusion, disorientation, dysarthria, headache, insomnia, lethargy, malaise, unsteadiness. *Ophthalmological*: blurred vision. *Psychiatric*: anxiety, depression, euphoria, panic attack, and paranoia. *Renal*: haematuria, UTI.
- *Serious—cardiovascular*: haemodynamic instability, syncope. *Neurological*: falls. *Psychiatric*: psychosis and suicidality. *Urological*: urinary retention.

Contraindications

Sativex®

- *Absolute*: hypersensitivity to cannabinoids or the preparations excipients, personal or family history (suspected or confirmed) of schizophrenia, attempted suicide, personality disorder, or other significant psychiatric disorder (other than depression related to MS).
- *Relative*: severe cardiovascular disease, epilepsy, patients with high falls risk, and those with a history of substance abuse.

Epidiolex®

- *Absolute:* hypersensitivity to cannabidiol or the preparations excipients.
- *Relative:* Epidiolex causes dose-related transaminitis. Elevated ALT >3× upper limit of normal occurred in 13%. Risk factors for transaminitis include: 1) concomitant valproate and clobazam use, increased dose, and baseline elevated transaminases; 2) individuals with pre-existing suicidal ideation.

Uses in special populations

- *Elderly*: elderly patients (up to 90 years old) have been included in clinical trials. They may be at increased risk of CNS side effects including sedation and transaminitis.
- *Pregnancy*: There is no conclusive evidence linking cannabinoids with foetal harm, but maternal cannabis use is associated with an increase in congenital malformation rate, stillbirth, and foetal growth impairment. It is difficult to differentiate the effects of cannabinoids and tobacco in these products. There is no data specifically looking at Epidiolex® or Sativex®. The manufacturer advises avoidance in pregnancy unless the benefits outweigh the risks.
- *Lactation*: There are minimal data available. In studies of cannabis smokers, the estimated daily THC intake for the infant corresponded to between 0.5–9% of the weight-adjusted maternal dose. A 1-year study has suggested that daily cannabis inhalation by breastfeeding mothers may impair an infant's motor development. Professional guidelines typically advise avoidance against use in breastfeeding mothers.

Efficacy

- *Dravet syndrome:* A double-blind, placebo-controlled trial of 120 children with Dravet syndrome and treatment-refractory seizures, treated patients with either Epidiolex® or placebo. The median monthly seizures reduced from 12.4 to 5.9 with Epidiolex® compared to 14.9 to 14.1 with placebo ($p = 0.01$).
- *Lennox–Gastaut syndrome:* A double-blind, placebo-controlled trial of 255 patients with Lennox–Gastaut syndrome, treated patients with either Epidiolex® or placebo. Patients in the 20 mg cannabidiol group experienced a median 42% reduction in drop attacks, compared to 17.2% with the placebo group ($p = 0.005$).
- *Neuropathic pain*: a small placebo-controlled trial of 66 patients with neuropathic pain of various aetiologies showed that Sativex® reduced pain scores and improved patients' well-being. A recent RCT of 339 participants with MS demonstrated that Sativex® had a small but significant effect over placebo in improving patients' pain scores (reduction in pain score by 0.79 on a 10-point scale, compared to placebo; $p = 0.038$). Sativex® was not found to be beneficial for treating painful diabetic neuropathy in a recent systematic review.
- *Spasticity*: The first major study to study the role of Sativex® was a 2004 double-blind, randomized control study that, in part, evaluated the reduction in spasticity. A total of 160 subjects were enrolled in the trial (80 active, 80 placebo). Subjects self-titrated up to a maximal permitted dose of 120 mg/THC per day. Subjects were assessed at 6 weeks.

Spasticity, as measured on a visual analogue scale (VAS), on a range of 0 to 100, decreased 31.2 points in the Sativex® group compared to 8.4 points in the placebo control ($p = 0.001$). This trial was followed by an open-label extension (OLE). A total of 137 patients continued into the OLE and were followed for a mean of 434 days. Sativex® demonstrated a clinically significant reduction in subjective spasticity, as measured by a sustained improvement in the VAS.

Dosing and monitoring

Dosing

Epidioloex®: Start treatment at 2.5 mg/kg twice daily, then increase in steps of 2.5 mg/kg twice daily every week as required up to a maximum of 10 mg/kg twice daily. (Note food may affect absorption)

Sativex®: Start with one spray actuation in the evening for the first 2 days of therapy; then two evening sprays for the next 2 days. Thereafter, the dose can be increased by one spray per day, up to a maximum daily total of 12 sprays. Dosing should be biased towards the evening administration, i.e. five sprays in the morning and seven sprays in the evening. Administration without food/fluid is advised to minimize the amount of swallowed drug. The minimum time between sprays is 15 min. A trial for 4 weeks is recommended.

Monitoring

Epidiolex® can cause a severe liver injury. Patients should have baseline liver function tests. These should be repeated at 1 month, 3 months, and 6 months after every dose change. Patients should have regular monitoring whilst on treatment. Treatment should be discontinued if transaminases are >3× the upper limit of normal and bilirubin is >2× upper limit of normal, or if transaminases are >5× upper limit of normal. Consider lower dosing and more frequent monitoring in patients at higher risk of hepatocellular dysfunction.

Pharmacokinetics and interactions

Pharmacokinetics

Epidiolex® Tmax occurs at 2.5–5 h. The oral bioavailability is ~6%. Bioavailability is reduced and Tmax increased if the medication is taken with food. The half-life is 56–61 h. Cannabidiol is predominantly metabolized by the cytochrome P450 system in the liver and, to a lesser extent, the gut. It is excreted in faeces in an inactive form.

Sativex® is absorbed rapidly through the oropharyngeal mucosa, achieving a maximal plasma concentration of THC at 45–120 min. Bioavailability is highly variable between patients due to unpredictable proportions of each dose being swallowed; when the drug is swallowed, it undergoes significant first-pass metabolism, which is otherwise bypassed via the oral mucosal route. Metabolism is hepatic, predominantly hydroxylation by CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The main metabolite of THC is the highly psychoactive 11-OH-THC, while the CBD component is primarily metabolized to 7-OH-CBD. Excretion is as metabolites in the faeces and urine. Extensive binding to fatty tissues results in a biphasic elimination half-life of 4 h for redistribution into fat and 24–36 h for terminal elimination.

Interactions

See Table 23.18.

Table 23.18 Interactions of cannabinoids

Medications which alter cannabinoid plasma levels	Medications whose plasma levels are altered by cannabinoids	Pharmacodynamic interactions
Levels decreased: CYP3A4 inducers, e.g. rifampicin, carbamazepine, St John's Wort **Levels increased:** CYP2C9 inhibitors, e.g. valproate, fluconazole; CYP3A4 inhibitors, e.g. ketoconazole	**Levels increased:** Epidiolex causes a 3× increase in the active metabolite of clobazam. CYP1A2 substrates, e.g. theophylline, caffeine, CYP2B6 substrates, e.g. bupropion, efavirenz, CYP2C9, e.g. phenytoing, UGT1A9 substrates, e.g. propofol, fenofibrate, and UGT2B7 substrates, e.g. lamotrigine, morphine, and lorazepam	**With anticholinergics:** increased risk of tachycardia **With CNS depressants:** increased sedation **With MAOIs:** increased risk of orthostatic hypotension **With valproate:** Epidiolex has an increased risk of hepatocellular dysfunction

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Carbamazepine and related anti-seizure medications

Carbamazepine, eslicarbazepine acetate, and oxcarbazepine are most commonly used in the management of focal epilepsy. Carbamazepine is also used first-line in the treatment of trigeminal neuralgia and vestibular paroxysmia, and second-line in the management of rare forms of TACs (SUNCT). The use of carbamazepine is complicated, to some extent, by its side effects and drug interaction profile, due, in part, to its active metabolite carbamazepine-10,11-epoxide. Eslicarbazepine acetate and oxcarbazepine are carbamazepine derivatives. Neither compound is metabolized to carbamazepine-10,11-epoxide. This reduces the risk of liver toxicity and haematological disorders. It also means there is little involvement of the cytochrome P450 enzyme system, and thus this decreases the level of autoinduction and interaction with other ASMs. Hence eslicarbazepine acetate and oxcarbazepine have similar actions to carbamazepine and can be used to manage focal epilepsy, and in RCTs of oxcarbazepine also trigeminal neuralgia when carbamazepine is not tolerated.

Of note, eslicarbazepine acetate has the added benefit that it only requires once-daily dosing, while carbamazepine is the only medication in this group that is available as a suppository. None of these agents can be given parenterally.

Uses

Licensed uses

In the UK/USA

1. Carbamazepine.
   - *Epilepsy*: carbamazepine is licensed for the treatment of generalized tonic–clonic and focal-onset seizures, with or without secondary generalization, in individuals of all ages.
   - *Trigeminal neuralgia*: carbamazepine is also licensed for the treatment of trigeminal neuralgia in individuals of all ages.
2. Eslicarbazepine acetate.
   - *Epilepsy*: in the US eslicarbazepine acetate is licensed as an adjunct for the treatment of focal-onset seizures, with or without secondary generalization, in individuals aged 4 years and older. In the UK it is licensed as monotherapy for the treatment of partial-onset seizures, in adults; and as an adjunct in individuals 6 years and older.
3. Oxcarbazepine.
   - *Epilepsy*: oxcarbazepine is licensed as a monotherapy (UK: age 6 years and older; USA: age 4 years and older) or an adjunct (UK: age 6 years or older; USA: age 2 years and older) for the treatment of focal-onset seizures, with or without secondary generalization.

Off-label uses

1. *Carbamazepine*: neuropathic pain, SUNCT, and vestibular paroxysmia.

Mechanism of action

The predominant mechanism of action is a use-dependent block of neuronal voltage-gated sodium channels. A reduction in glutamate release has also been shown. Carbamazepine may also stabilize neurons by exerting an inhibitory action on L-type calcium channels.

Toxicity and side effects

Many of the side effects are shared within this group of drugs. Theoretically, eslicarbazepine acetate may result in fewer side effects, as peak levels are lower than that of oxcarbazepine.

- *Common—Dermatological*: rash. Dermatological manifestations are commoner in patients of Han Chinese or Thai origin associated with HLA-B*1502 allele. This can be tested for, if the allele is identified carbamazepine should be avoided. Skin reactions are less common with eslicarbazepine acetate (1.1%) and oxcarbazepine (5%), compared with carbamazepine (15%). ~25% of patients experiencing a rash with carbamazepine will also experience one with oxcarbazepine. *Endocrine*: carbamazepine and related ASMs share an ADH-like effect, resulting in fluid retention, hyponatraemia, oedema, and weight increase. *Gastrointestinal*: dry mouth, increased γ glutamyl transferase and alkaline phosphatase (ALP), nausea, and vomiting. With carbamazepine suppositories, rectal irritation can occur. *Neurological*: ataxia, blurred vision, diplopia, drowsiness, dizziness, fatigue, and headache are relatively common and most likely due to excessive action at voltage-sensitive sodium channels.
- *Serious—cardiovascular*: arrhythmias and AV block can occur. Thromboembolism and an exacerbation of coronary artery disease has been reported with carbamazepine. *Dermatological*: angio-oedema, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been reported. *Gastrointestinal*: hepatitis and pancreatitis rarely occur. *Haematological*: blood dyscrasias, including aplastic anaemia and pancytopenia, can occur. Exacerbations of porphyria have been seen with carbamazepine. *Immunological*: Anaphylaxis, a multiorgan hypersensitivity syndrome and systemic lupus erythematosus (SLE) have been reported. *Neurological:* NMS, aseptic meningitis with myoclonus, and peripheral eosinophilia. *Psychiatric*: rarely acute psychosis. *Renal:* Renal failure and tubulointerstitial nephritis.

Contraindications

- *Absolute*: these ASMs are ineffective and can even worsen some primary generalized seizure types, i.e. absence, atonic, and myoclonic seizures. They should be avoided in patients with AV conduction block. Avoid carbamazepine in patients with porphyria.
- *Relative*: these ASMs should be used with caution in patients with bone marrow depression, open-angle glaucoma, pre-existing hyponatraemia, and heart failure. Carbamazepine should be avoided if the patient has developed previous hypersensitivity reactions to ASMs in this group. Eslicarbazepine acetate and oxcarbazepine should be used with caution if there has been previous hypersensitivity reaction to carbamazepine. Reduced doses should be used in those with hepatic and/or renal impairment. The manufacturers of eslicarbazepine acetate recommend it is avoided in severe hepatic impairment and in renal impairment with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.

- Eslicarbazepine acetate: if the eGFR is 30–60 mL/min/1.73 m^2, then the initiation, titration, and maintenance dose should be reduced by 50%.
- Oxcarbazepine: if the eGFR is <30 mL/min/1.73 m^2, halve the initial dose, and increments should occur slowly in at least once-weekly intervals.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens. Pharmacodynamic drug interactions are more likely; the risk of symptomatic hyponatraemia is increased in the elderly who may also take non-steroidal anti-inflammatory drugs (NSAIDs) or sodium-lowering antihypertensives.
- *Pregnancy*: for carbamazepine, there is clear evidence, from human studies, of an increased rate of foetal teratogenicity, this appears to be dose related. Use in pregnancy involves weighing up the potential benefits and side effects (see Anti-seizure medications in young women, p. 38). Pregnant patients should be prescribed folic acid throughout pregnancy, and vitamin K prior to birth to reduce the risk of haemorrhage. Elimination of carbamazepine can increase during pregnancy. Total plasma concentration can be reduced by up to 40%. However, for many women, carbamazepine levels may not decline or decline by an average of only 9–12%.

Eslicarbazepine acetate and oxcarbazepine's side effects in pregnancy have not been adequately explored, although a similar level of teratogenicity to carbamazepine can be expected. Similar precautions to those taken when using carbamazepine are recommended.

- *Lactation*: plasma levels of carbamazepine and oxcarbazepine in infants are 10–20% of those of their mothers (figures for eslicarbazepine acetate are not known). If used, infants should be monitored for potential side effects such as gastrointestinal disturbance, seizures, respiratory depression, and drowsiness. If identified, switch to alternative methods of feeding.

Efficacy

1. Carbamazepine.

- *Epilepsy*: carbamazepine is one of the most effective drugs used in focal-onset epilepsy. Recent studies demonstrate that it is at least as effective as the newer agents. Its main disadvantage, when compared to other ASMs, e.g. lamotrigine, is the rate of treatment failures due to adverse events. About a third of patients experience symptoms of lethargy and an allergic rash, both approximately twice as common than in patients initiated on lamotrigine. Five years after starting treatment with carbamazepine as a monotherapy, 45% of patients will enjoy continuing treatment success; 30% of the initial population will have stopped treatment because of side effects, and 25% because of failure of seizure control.
- *Trigeminal neuralgia*: the majority of data for the efficacy of carbamazepine in trigeminal neuralgia are from small open-label

studies conducted in the 1960s. Two RCTs, with the majority of patients suffering from trigeminal neuralgia (98 participants), showed carbamazepine provided better analgesia than placebo, with an number needed to treat (NNT) of 2 (95% CI 1–2). It is generally recognized (including by NICE) that there is a lack of good trial evidence for the efficacy of carbamazepine in neuropathic pain. Both the European Federation of Neurological Societies (EFNS) and NICE recommend carbamazepine first-line for trigeminal neuralgia. The EFNS does not recommend carbamazepine be used for any other type of neuropathic pain disorder.

2. Eslicarbazepine acetate.

- Eslicarbazepine acetate use in focal-onset seizures has been the subject of a recent Cochrane review. It concluded that, as an adjunct, eslicarbazepine acetate can reduce seizure frequency in the short term. However, there are little data on longer-term outcomes. A further integrated analysis of three phase 3, double-blind, placebo-controlled studies in patients with focal-onset epilepsy refractory to up to three medications showed that over a third of patients can experience at least a 50% reduction in seizure frequency when eslicarbazepine acetate is used as an adjunct.

3. Oxcarbazepine.

- A multinational, multicentre, double-blind trial investigated the effectiveness of oxcarbazepine in refractory focal epilepsy. It demonstrated a reduction in seizure frequency in 40% at doses of 1.2 g and 50% at doses of 2.4 g daily. The frequency of rash with oxcarbazepine is two-thirds lower than with carbamazepine.

Dosing and monitoring

Dosing

1. *Carbamazepine (all indications)*: start treatment at 2 to 3 mg/kg/day (100 to 200 mg/day) and increase every 1–2 weeks by 100–200 mg in divided doses. The sustained-release preparations require bd dosing, and standard preparations three divided daily doses. For epilepsy, the dose in adults is normally titrated up to about 10 mg/kg/day (800–1200 mg/day), although this can go up to 2 g/day, if required. For other indications, the usual maintenance dose is 600–800 mg/day. After 2 to 3 months of treatment, serum concentrations may decrease due to hepatic enzyme autoinduction and dose may need to be increased further to 15–20 mg/kg/day.
2. *Eslicarbazepine acetate*: start treatment at 400 mg daily. The tablets can be increased by 400 mg increments 1- to 2-weekly as tolerated up to 1.6 g, although 800 mg once daily is typically a sufficient maintenance dose.
3. *Oxcarbazepine (all indications)*: start treatment at 300 mg bd; increase weekly in steps of up to 600 mg to a maximum dose of 2.4 g in 2 to 3 divided daily doses. The usual daily dosage range in adults is between 0.6 g and 2.4 g in two divided doses.

Monitoring

- *Carbamazepine*: prior to initiation of treatment, FBC, and renal and liver function should be assessed. An FBC is recommended 2-weekly for 2 months, then 3-monthly throughout treatment. Liver and renal function should be assessed 6- to 12-monthly throughout treatment.
- *Eslicarbazepine acetate/oxcarbazepine*: before initiation of treatment, liver and renal function tests are recommended. These should be repeated yearly.

Therapeutic drug monitoring

- Optimum seizure control when used in monotherapy for carbamazepine occurs at plasma concentrations of 4–12 mg/L, and for eslicarbazepine acetate and oxcarbazepine at 3–35 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oxcarbazepine and eslicarbazepine acetate are both prodrugs which are converted to eslicarbazepine in the liver.

1. *Carbamazepine*: oral bioavailability of carbamazepine is ~85%. Peak plasma concentrations are reached at different time points, depending on the formulations used: conventional tablets at ~12 h, chewable tablet at ~6 h, and liquid at ~2 h. This is not affected by food co-ingestion. Bioavailability varies between preparations. Due to reduced bioavailability, a 125 mg suppository is equivalent to a 100 mg oral tablet. Steady-state plasma concentrations are reached within 1–2 weeks, depending on autoinduction of cytochrome P450 enzymes and interaction with other ASMs. 70–80% of carbamazepine is bound to plasma protein. Carbamazepine is metabolized by the liver into a number of derivatives, including the pharmacologically active carbamazepine-10,11-epoxide. The metabolites are then excreted ~70% in the urine and ~30% in the stool. The half-life varies with the duration of therapy. At initiation, the half-life is 25 to 65 h; after a few weeks, hepatic enzyme autoinduction means that the half-life decreases to 12–17 h.
2. *Eslicarbazepine acetate*: eslicarbazepine acetate is a prodrug, rapidly converted by hepatic first-pass metabolism to the active metabolite eslicarbazepine. The bioavailability is >90%, and T_{max} occurs 2–3 h post-dose. The half-life of eslicarbazepine acetate is 2 h; that of the active metabolite eslicarbazepine is 20–24 h. A third of eslicarbazepine is conjugated with glucuronic acid in the liver. The majority of the rest is excreted unchanged; >90% is excreted renally.
3. *Oxcarbazepine*: oral bioavailability is ~100%. T_{max} occurs 3–6 h post-dose. This is rapidly metabolized by the liver into its active metabolite 10-hydroxycarbazepine (also known as eslicarbazepine), which, in turn, reaches its steady-state plasma level in 2–3 days. 10-hydroxycarbazepine is metabolized by conjugation with glucuronic acid in the liver, and, unlike with carbamazepine, there is no autoinduction; hence pharmacokinetics are linear. The half-life of oxcarbazepine is 2 h, and that of 10-hydroxycarbazepine 8–15 h. Over 95% of the drug and its metabolites are excreted in the urine.

Interactions

See Table 23.19.

Table 23.19 Interactions of carbamazepine and related ASMs

Medications which alter ASM plasma levels	Medications whose plasma levels are altered by ASM	Pharmacodynamic interactions
1. Carbamazepine **Levels decreased:** CYP3A4 inducers, e.g. oxcarbazepine and rifampicin **Levels increased:** CYP3A4 inhibitors, e.g. cimetidine, clarithromycin, and fluconazole	**1. Carbamazepine** **Levels decreased:** CYP3A4 substrates, e.g. amitriptyline, benzodiazepines, ketoconazole,* and quetiapine* **Levels increased:** verapamil.	**1. Carbamazepine with lamotrigine and levetiracetam:** headache, nausea, and ataxia
2. Eslicarbazepine acetate **Levels decreased:** carbamazepine, phenytoin, and topiramate	**2. Eslicarbazepine acetate** **Levels decreased:** lamotrigine, simvastatin, topiramate, valproate, and warfarin Levels increased: phenytoin.	**2. Eslicarbazepine acetate:** nil
3. Oxcarbazepine **Levels decreased:** carbamazepine, lacosamide, oral contraceptives, phenobarbital, phenytoin, and verapamil. **Levels increased:** viloxazine	**3. Oxcarbazepine** **Levels decreased:** carbamazepine, felodipine, lamotrigine, levetiracetam, rufinamide, and topiramate **Levels increased:** phenobarbital and phenytoin	**3. Oxcarbazepine** **With lithium and lamotrigine:** enhanced neurotoxicity

* As a result of the magnitude of the interaction between carbamazepine and ketoconazole and between carbamazepine and quetiapine whereby ketoconazole and quetiapine plasma levels are decreased to almost non-detectable values, these drug combinations can be considered contraindicated.

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Catechol-O-methyltransferase inhibitors

Catechol-*O*-methyltransferase (COMT) inhibitors have been used in the treatment of Parkinson's disease (PD) since the mid-1990s. They include entacapone, opicapone, and tolcapone; tolcapone is considered second line due to the rare risk of severe liver dysfunction. COMT inhibitors are used as an adjunct to levodopa therapy, particularly in patients with motor fluctuations, as they may improve the wearing-off phenomenon and permit a reduction in the required levodopa dose.

Uses

Licensed uses

In the UK/USA

- *PD.*

1. *Entacapone* is licensed as an adjunct to levodopa for the treatment of end-of-dose motor fluctuations, or 'wearing off' effect in patients with PD aged 18 years or older and in patients who have been taking a total daily dose of levodopa of 600 mg or less without dyskinesias.
2. *Opicapone* is licensed as an adjunct to levodopa in patients with Parkinson's disease aged 18 years and older and end-of-dose motor fluctuations ('OFF episodes').
3. *Tolcapone* is licensed as an adjunct to levodopa therapy in patients with levodopa-responsive PD who are intolerant of, or have failed to show improvement with, an alternative COMT inhibitor in individuals aged 18 years and older.

Off-label uses

- None.

Mechanism of action

When levodopa is taken with a peripheral dopa-decarboxylase inhibitor, such as carbidopa, metabolism by COMT (found in the liver, gastrointestinal tract, and erythrocytes) becomes the major pathway of levodopa metabolism. Selective reversible inhibition of peripheral COMT by entacapone and tolcapone results in increased bioavailability of levodopa by preventing metabolism to 3-*O*-methyldopa, providing increased dopaminergic input to the striatum. As well as inhibiting peripheral COMT, tolcapone also acts to inhibit central COMT; the significance of this is unclear.

Toxicity and side effects

- *Common—Cardiovascular*: orthostatic hypotension and syncope. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, gastritis, peptic ulcer disease, nausea, taste disturbance, and vomiting. *Genitourinary*: urine discoloration (red-brown). *Neurological*: dizziness, dyskinesia (managed with 10–30% reduction in levodopa dose), hallucinations, somnolence, and weakness. *Respiratory*: dyspnoea.

- *Serious—Gastrointestinal*: abnormal LFTs (rarely fulminant hepatic failure with tolcapone), retroperitoneal fibrosis. *Musculoskeletal*: rhabdomyolysis. *Neurological*: neuroleptic malignant-like syndrome on withdrawal. *Psychiatric:* suicide, hallucinations. *Respiratory*: pulmonary fibrosis.

Patients may experience increased dopaminergic side effects (e.g. dyskinesia, hypersomnolence, postural hypotension, etc.), due to the increased serum concentration of levodopa while on a COMT inhibitor. Reduction in levodopa dose may help in this instance and should be tapered gradually with the supervision from a healthcare provider.

Patients may have dark coloration appear in saliva, urine, or sweat while taking carbidopa, levodopa, and entacapone together.

Contraindications

- *Absolute*: known hypersensitivity to COMT inhibitor, severe liver, or biliary disease, phaeochromocytoma, previous NMS, and rhabdomyolysis.
- *Relative*: concurrent non-selective MAOI use due to theoretical risk of excess catecholinergic activity. No dosage alteration is required in renal impairment. Monitor closely in cases of mild-to-moderate hepatic impairment, although no dose alteration is routinely recommended.

Use in special populations

- *Elderly*: no dose adjustment is routinely required.
- *Pregnancy*: animal reproduction studies report adverse events. There is a lack of safety data for use in pregnancy. The manufacturers advise avoidance, where possible, in this patient group.
- *Lactation*: While levodopa has been detected in human milk, excretion of COMT inhibitors in breast milk is not known. The manufacturers advise avoidance, where possible, in nursing mothers.

Efficacy

- *Entacapone*: STRIDE-PD (STalevo Reduction in Dyskinesia Evaluation) was a double-blind RCT comparing the effect of Stalevo® (levodopa/carbidopa/entacapone) to levodopa/carbidopa in patients with early PD who had not previously been treated with levodopa and did not have motor complications. Although outcomes were improved in both groups (UPDRS-II and III), no significant difference was noted between the groups. The LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) study was a double-blind RCT ($n = 687$) which randomized patients to rasagiline (1 g/day), entacapone (200 mg with each levodopa dose), or placebo over an 18-week period. Thirteen per cent of patients did not complete the study, due to withdrawal of consent and adverse events. The trial showed a significant increase in 'on' time in both rasagiline and entacapone arms (0.85 h vs. placebo 0.03 h; $p = 0.0005$) and reduction in 'off' time (−1.18 h rasagiline and −1.2 h entacapone vs. placebo −0.4 h; $p = 0.0001$, $p < 0.0001$, respectively).

- *Opicapone:* two double-blind, randomized, placebo-controlled trials of opicapone as an adjunct to levodopa in patients with Parkinson's disease demonstrated that opicapone was significantly more effective than placebo at reducing OFF time. A pooled analysis of the two trials demonstrated that the absolute reduction in daily OFF time was –58.1 (–84.5, –31.7) min ($p < 0.0001$) for the 50 mg dose, when compared to placebo.
- *Tolcapone*: a double-blind, placebo-controlled trial of tolcapone as an adjunct to levodopa ($n = 298$) found the treatment group had a significant reduction in levodopa usage and improvement in motor scores (100 mg tds, $p < 0.05$; 200 mg tds, $p < 0.01$). Activities of daily living, as part of the UPDRS, was the primary outcome measure and was found to have significant improvements from baseline in both tolcapone groups, compared to placebo ($p < 0.01$). Greatest effect was noted in those with the most severe impairment at baseline. The most important non-dopaminergic side effect was diarrhoea.

The MDS review found all of the COMTi efficacious as a symptomatic adjunct to levodopa in patients with motor fluctuations. There is no evidence that use early in the disease course prevents or delays motor complications.

Dosing and monitoring

Dosing

- *Entacapone*: start treatment at 200 mg, taken with each levodopa dose. Maximum dose is 2 g/day (ten tablets). Levodopa dose often needs to be reduced by approximately one-third, or the dosing interval may need to be extended.
- *Opicapone*: start treatment at 50 mg once nocte, at least 1 h before or after levodopa preparations.
- *Tolcapone*: start treatment at 100 mg tds. Only in exceptional circumstances can this be increased to 200 mg tds. If there is no clinical benefit within 3 weeks, it should be stopped.

Monitoring

- *Entacapone/opicapone*: routine monitoring of liver function is not necessary.
- *Tolcapone*: LFTs are measured every 2 weeks for the first year of treatment, 4 weeks for the next 6 months, and every 8 weeks thereafter.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.20.
Interactions See Table 23.21.

Table 23.20 Pharmacokinetics of COMT inhibitors

	Entacapone	Tolcapone	Opicapone
Main routes of administration	PO	PO	PO
Oral bioavailability	35%	65%	~20%
T_{max}	1 h	2 h	1–2.5 h
Protein binding	98%	99.8%	99.9%
Time to steady state	2–7 days	2–10 days	~14 days
Metabolism	Hepatic CYP2C9	Hepatic	Hepatic
Pharmacologically active metabolites	Yes (*cis*-isomer)	No	No
Elimination half-life	3 h	2–3 h 40% faeces	0.7–3.2 h
Elimination routes	80–90% faeces 10–20% urine	60% urine	60–75% faeces 10–20% urine

Table 23.21 Interactions of COMT inhibitors

Medications which alter COMT inhibitor plasma levels	Medications whose plasma levels are altered by COMT inhibitors	Pharmacodynamic interactions
Levels decreased: iron (oral) with entacapone	**Levels increased:** warfarin with entacapone	**With other CNS depressants:** may increase risk of CNS depression. **Caution advised with MAOIs, TCAs, SNRIs, and drugs metabolized by COMT, e.g. adrenaline:** limited experience with these drugs (selegiline can be used, but maximum dose 10 mg)

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CGRP monoclonal antibodies

Calcitonin gene-related peptide (CGRP) is a polypeptide neurotransmitter implicated as a key component of migraine pathophysiology. The CGRP monoclonal antibodies are a group of recently released medications that target CGRP or the CGRP receptor. They include eptinezumab, erenumab, fremanezumab, and galcanezumab. Erenumab, the only antibody in this group to target the CGRP receptor rather than CGRP itself, was the first drug to receive FDA approval in 2018. This group of medications are available for intravenous or subcutaneous infusion. They have proved to be highly effective preventative agents for migraine.

Uses

Licensed uses

In the UK/USA (licensing is the same)

- Migraine: All of the CGRP monoclonal antibodies are licensed for the preventative treatment of migraine in individuals aged 18 years and older.

Off-label uses

- Acute treatment for migraine and cluster headache

Mechanism of action

This group of medications are monoclonal antibodies, which block the effects of CGRP in the trigeminovascular system. Eptinezumab, fremanezumab, and galcanezumab directly bind to CGRP, whilst erenumab blocks the CGRP receptor. Activation of the CGRP receptor triggers a cascade of events that initiate and perpetuate migraine attacks.

Toxicity and side effects

- *Common—Dermatological:* Injection site reactions, pruritus, and rash. *Gastrointestinal:* Constipation (reported with erenumab—usually resolves within 3 months). *Neurological:* Vertigo (reported with galcanezumab).
- *Serious—Immunological:* Rarely anaphylaxis and angioedema.

Contraindications

- *Absolute*: hypersensitivity to the medication or its excipients.
- *Relative*: hepatic and renal impairment are not expected to affect the pharmacokinetics of these molecules.

Use in special populations

- *Elderly*: clinical trials of CGRP monoclonal antibodies did not include significant numbers of participants over the age of 65. Side effects are more common in the elderly, hence clinicians should be cautious when using CGRP monoclonal antibodies in this group.
- *Pregnancy*: There is limited data from human studies. It is likely that all of the monoclonal antibodies will cross the placental barrier, leading to foetal exposure. There is no evidence of adverse events from animal studies. Use only if potential benefits outweigh risks.

- *Lactation*: There is limited data from human studies. IgG antibodies are present in human breastmilk in the first few days after birth. After this, the risk of exposure reduces significantly. Patients should not receive monoclonal antibodies shortly after delivery if they are breastfeeding. Use after the first week could be considered if benefits outweigh risks.

Efficacy

Eptinezumab: A phase 3 randomized, double-blind, placebo-controlled trial evaluated the efficacy of eptinezumab in the treatment of chronic migraine. The mean monthly migraine days were significantly reduced by 7.7 days with 100 mg eptinezumab and 8.2 days with 300 mg eptinezumab, compared to 5.6 days with placebo ($p < 0.0001$ for both doses).

Erenumab: Several phase 3, double-blind, randomized, placebo-controlled studies have demonstrated that erenumab significantly reduced monthly migraine days compared to placebo, including in groups of patients who have previously failed prior prophylactic treatments. A phase 3 randomized controlled trial of patients with episodic migraine (4–14 migraine days a month), who had trialled 2–4 previous migraine prophylactics, demonstrated that 30% of patients who took erenumab had a 50% or greater reduction in mean monthly migraine days, compared with 14% with placebo ($p = 0.002$).

Fremanezumab: Several phase 3 randomized, placebo-controlled trials have demonstrated that fremanezumab is effective in the treatment of chronic and high-frequency episodic migraine. A phase 3, double-blind, randomized, placebo-controlled trial examined the efficacy of fremanezumab for the treatment of patients who had episodic or chronic migraine and who had failed two to four preventative treatments. There was a statistically significant reduction in mean monthly migraine days of 3.7 days with quarterly fremanezumab compared to 3.1 days with placebo ($p < 0.0001$), and a reduction of 4.1 days with monthly fremanezumab compared to 3.5 days with placebo ($p < 0.0001$).

Galcanezumab: Several phase 3 randomized, placebo-controlled trials have demonstrated that galcanezumab is effective in the treatment of chronic and high-frequency episodic migraine. A phase 3, randomized, double-blind, placebo-controlled trial examined the efficacy of galcanezumab for the treatment of episodic and chronic migraine in patients who were refractory to two to four preventative treatments. There was a statistically significant reduction in mean monthly migraine days of 4.1 days with galcanezumab at 120 mg/month compared to 1 day with placebo ($p < 0.0001$).

Dosing and monitoring

Dosing

Eptinezumab: Administer 100 mg by intravenous infusion every 12 weeks. 300 mg every 12 weeks can be used if this is ineffective.

Erenumab: Administer 70 mg by subcutaneous injection every 4 weeks. 140 mg every 4 weeks can be used if this is ineffective.

Fremanezumab: Fremanezumab is administered by subcutaneous injection. It can be given as either 225 mg once monthly, or 675 mg thrice monthly.

Galcanezumab: Galcanezumab is administered by subcutaneous injection. Administer 240 mg as a loading dose, followed by 120 mg every 3 months.

Monitoring

No routine monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.22.

Table 23.22 Pharmacokinetics of CGRP monoclonal antibodies

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Main routes of administration	IV	SC	SC	SC
Bioavailability	100%	82%	55–66%	50–100%
T_{max}	30 min	70 mg: 6.1 days. 140 mg 15.8 days	5–7 days	5 days
Metabolism	The CGRP monoclonal antibodies are metabolized by proteolytic enzymes, into inactive metabolites			
Elimination half-life	27 days	28 days	30 days	27 days

NA, information not available; IV, intravenous; SC, subcutaneous.

Interactions

No significant interactions have been reported or would be predicted for this class of drugs.

References

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Complement inhibitors: Eculizumab and ravulizumab

Eculizumab and ravulizumab are monoclonal antibodies that inhibit complement activation by binding to complement protein C5, thereby preventing it from generating the terminal complement complex. The FDA first approved eculizumab for the treatment of AChR antibody-positive myasthenia gravis in 2017. Ravulizumab received the same approval in 2022. Both have subsequently been approved for the treatment of patients with aquaporin 4 positive neuromyelitis optica spectrum disorder (NMOSD). They are administered by intravenous infusion. Ravulizumab differs from eculizumab due to a targeted substitution of amino acids in the complement binding and FcRn region of the antibody. This allows for faster recycling of ravulizumab into blood vessels by the FcRn receptor pathway. Consequently, eculizumab needs to be administered on a two-weekly basis whilst ravulizumab can be administered on an eight-weekly basis.

Uses

Licensed uses

In the UK/USA (Licensing is the same)

- Myasthenia gravis: Eculizumab and ravulizumab are both licensed for the treatment of AChR antibody-positive generalized myasthenia gravis in individuals aged 18 years and older.
- NMOSD: Eculizumab and ravulizumab are both licensed for the treatment of AQP4 positive NMOSD in individuals aged 18 years and older.

Off-label uses

- Guillain–Barré syndrome and Multifocal motor neuropathy

Mechanism of action

Both eculizumab and ravulizumab are monoclonal antibodies that bind the complement protein C5. They prevent cleavage of C5 into C5a and C5b, thereby preventing activation of the terminal C5b-9 complex. This prevents deposition of C5b-9 deposition at the neuromuscular junction in myasthenia gravis and, at sites containing aquaporin 4 in the central nervous system, reducing the damage done by this complex and improving the clinical symptoms of several autoimmune diseases.

Toxicity and side effects

- *Common—Dermatological:* Herpes simplex infections, infusion reactions, and rash. *Gastrointestinal:* Constipation. *Musculoskeletal:* Back pain. *Neurological:* Headache and fatigue. *Respiratory:* Cough, nasopharyngitis, and respiratory tract infections.
- *Serious—Infectious:* Meningococcal sepsis, as well as other bacterial and fungal infections, are more common during treatment. Patients should have their vaccination status reviewed in advance of treatment. Patients should receive vaccination against *Neisseria meningitides* at least 2 weeks prior to treatment.

Contraindications

- *Absolute*: hypersensitivity to the medication or its excipients. Patients with unresolved *Neisseria meningitides* infection or who have not been vaccinated for the same infection.
- *Relative*: Renal impairment does not significantly affect the pharmacokinetics or side effect profile of either eculizumab or ravulizumab; neither medication has been assessed for significant hepatic impairment. Hepatic impairment is unlikely to have a significant effect on the pharmacokinetics or safety profile of either medication. However, given the lack of data patients should be monitored closely.

Use in special populations

- *Elderly*: no dose adjustments are recommended in the elderly population, but the elderly may be predisposed to infectious side effects so treatment should be monitored closely.
- *Pregnancy*: Both antibodies are likely to cross the placenta. In mice studies, higher antibody doses were associated with a higher degree of retinal dysplasia and a slight decrease in the survival rates for male rodents. Post-marketing data from over 300 patients having taken eculizumab during pregnancy did not identify any significant safety concerns. No safety concerns have yet been reported with ravulizumab. Use if potential benefits outweigh the risks.
- *Lactation*: Both medications are likely to be present in breastmilk, but there is unlikely to be significant absorption from an infant's gastrointestinal tract. There is no data on outcomes from infants exposed to either medication during nursing. Infants should be monitored for side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

Myasthenia gravis:

1. *Eculizumab*—A randomized, double-blind, placebo-controlled trial evaluated the use of eculizumab in patients with AChR antibody-positive generalized myasthenia gravis, who had proved refractory to two previous immunotherapies. There was no significant change in the myasthenia gravis activities of daily living scale (MG-ADL) between the treatment and placebo groups. In most other indexes of myasthenia gravis severity, the eculizumab group performed better than placebo at 26 weeks.
2. *Ravulizumab*—A randomized, double-blind, placebo-controlled trial evaluated the use of ravulizumab in patients with AChR antibody-positive generalized myasthenia gravis. Patients were on stable immunosuppressive treatment prior to entering the trial. There was a significant improvement in the MG-ADL scale at 26 weeks (–3.1 vs. –1.4 with placebo, $p < 0.001$).

NMOSD:

1. *Eculizumab*—The PREVENT study was a double-blind, randomized, placebo-controlled time-to-event trial, which evaluated the efficacy

of eculizumab for the treatment of patients with aquaporin 4 positive NMOSD. Patients needed to be on stable immunosuppressive therapies and have had at least one relapse in the last year. The primary endpoint of relapse occurred in 3% of treated patients and 43% of patients on placebo (HR 0.06 p <0.001).

2. *Ravulizumab*—A randomized, double-blind, placebo-controlled trial evaluated the use of eculizumab in patients with aquaporin 4 positive NMOSD. Patients needed to be on stable immunosuppressive therapies and have had at least one relapse in the year prior to screening. The relapse risk reduction was 98.6% in the treatment group when compared to the PREVENT placebo group (p <0.0001) (The PREVENT placebo group was used as an external comparator). No patients in the treatment group had a relapse during 84 patient-years of treatment.

Dosing and monitoring

Dosing

Both medications are administered by intravenous infusion.

Eculizumab: Start treatment at 900 mg weekly for the first 4 weeks. Administer 1200 mg at week five and every 2 weeks thereafter.

Ravulizumab: Dosing is guided by weight: Individuals who weigh 40–60 kg should be given a 2400 mg loading dose followed by a 3000 mg maintenance dose at, 2 weeks. Individuals who weigh between 60 and 100 kg should be given a 2700 mg loading dose followed by a 3300 mg maintenance dose at 2 weeks. Individuals who weigh >100 kg should be given a 3000 mg loading dose followed by a 3600 mg maintenance dose at 2 weeks. Maintenance doses should be repeated at 8-week intervals.

Monitoring

There are no specific monitoring requirements.

Pharmacokinetics and interactions

Pharmacokinetics

Steady state occurs 4 weeks after starting eculizumab and after the first dose of ravulizumab. Both monoclonal antibodies are metabolized in a similar fashion to endogenous immunoglobulin into inactive peptides and amino acids. Both medications demonstrate dose-proportional pharmacokinetics. The terminal elimination half-life is 11–17 days for eculizumab and 50–64 days for ravulizumab.

Interactions

IVIg may reduce serum concentrations of both medications.

References

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Corticosteroids

Corticosteroids (CS) are hormones synthesized from cholesterol in the adrenal cortex. They have diverse physiological and molecular effects on the body. They can be broadly divided into two classes—glucocorticoids (GCs), which control carbohydrate and fat metabolism, and mineralocorticoids (MCs) which principally regulate sodium balance (see Table 23.23). The anti-inflammatory properties of GCs are exploited in neurology, and there are many empirical and evidence-based uses in the field. GCs often form part of immunosuppressive treatment regimens, both in the induction phase and typically at a lower dose in the maintenance phase. Unfortunately, their diverse side effect profile limits their long-term use.

Several qualitative and clinically relevant differences exist between CS. Cortisol is made by the zona fasciculata of the adrenal cortex and is the active endogenous GC. This is metabolized to cortisone which is largely inactive. Hydrocortisone is the synthetic form of cortisol. It is available as an oral formulation but has a short half-life requiring multiple daily doses. It can also be given IV on a short-term basis when a parenteral route of administration is required. Prednisolone is the most administered oral steroid. It is the active metabolite of prednisone (itself inactive). Methylprednisolone is often used as IV pulsed therapy for suppression of inflammatory disorders, e.g. MS. Dexamethasone possesses negligible MC activity and therefore is highly useful in clinical situations in which fluid retention would be deleterious. Aldosterone is the active endogenous MC, and fludrocortisone is its synthetic, orally administered analogue. For a comparison of relative GC and MC effects of commonly used CS, see Table 23.23.

Uses

1. *Methylprednisolone and prednisolone*: Licensed neurological indications include acute exacerbations of MS, demyelinating neuropathy, and

Table 23.23 Relative glucocorticoid (GC) and mineralocorticoid (MC) effects of commonly used corticosteroids

Drug	GC effect	MC effect	Anti-inflammatory dose equivalent to 5 mg prednisolone
Hydrocortisone	1	1	20 mg
Prednisolone	4	0.8	5 mg
Methylprednisolone	5	–	4 mg
Dexamethasone	30	–	750 micrograms
Fludrocortisone	10	125	NA

NA, information not available.

cerebral oedema. In practice, these medications are frequently used for a broad range of conditions off-label. In general, IV pulsed methylprednisolone is used acutely for any condition in which a rapid and intense CS effect is required. Oral prednisolone is used in the management of all conditions deemed likely to benefit from short- or long-term GC therapy. A (non-exhaustive) list of these conditions is given below:

- ADEM
- Autoimmune limbic encephalitis
- Behcet's
- Bell's palsy
- CIDP
- DMD
- GCA
- IBM (trial)
- LEMS
- MOH
- MS
- MG
- Neurolupus
- NMO
- Neurosarcoidosis
- Optic neuritis
- PM/DM
- Sjogren's syndrome
- Susac's syndrome
- TACs
- TM
- Status migrainosus
- Vasculitis.

2.*Dexamethasone.*

Licensed uses

In the UK/USA

- *Cerebral oedema*: in the UK, dexamethasone is licensed for use as an adjunct in the control of raised intracranial pressure (ICP) secondary to cerebral tumours and infantile spasms in individuals of all ages. In the USA, it is licensed for use in the management of cerebral oedema associated with a primary or metastatic brain tumour, craniotomy, or head injury in individuals of all ages.

Off-label uses

- Adjunctive treatment in acute bacterial meningitis and varicella-zoster virus (VZV) encephalitis.

3. *Fludrocortisone*

- See further information on p. 580.

Mechanism of action

- *Neuro-inflammatory conditions*: the anti-inflammatory properties of GCs arise through multiple mechanisms; they bind to intracellular cytoplasmic receptors, inducing a range of cellular responses, including modification of transcription and protein synthesis. This leads to modulation of leucocyte activation, migration, cytokine production, and overall suppression of humoral responses.

- *Cerebral oedema*: dexamethasone reduces cerebral oedema formation by upregulation of cell membrane tight junctions, thereby reducing endothelial permeability at the blood–brain barrier. Several mediators are thought to be involved via steroid–receptor complex effects on gene transcription. These include downregulation of vascular endothelial growth factor (VEGF) production, phospholipase A2 inhibition, and stabilization of lysosomal membranes.

Toxicity and side effects

Short courses of steroids are typically associated with minor and transient side effects. These include dyspepsia, sleep disturbance, mood changes, confusion, infection risk, and impaired glucose tolerance. Repeated courses, higher doses, and chronic use are associated with the following side effects:

- *Common—Cardiovascular*: hypertension. *Dermatological*: acne, ecchymosis, impaired healing, and skin atrophy. *Endocrine*: Cushingoid appearance, hypokalaemia, impaired glucose tolerance, increased appetite, sodium and water retention, and weight gain. *Gynaecological*: menstrual irregularity. *Haematological*: leucocytosis. *Immunological*: hypersensitivity and increased susceptibility to infections. *Musculoskeletal*: osteoporosis and proximal myopathy. *Ophthalmological*: subcapsular cataracts. *Psychiatric*: affective disorder.
- *Serious—Cardiovascular*: deterioration in cardiac failure. *Dermatological*: Kaposi's sarcoma. *Endocrine*: adrenal insufficiency on withdrawal of treatment. *Gastrointestinal*: gastrointestinal ulceration and pancreatitis. *Musculoskeletal*: avascular necrosis of the hip is an important, but rare, potential side effect, which can occur after a single course. *Immunological*: anaphylaxis, increased susceptibility to infections, and reactivation of latent tuberculosis (TB). *Neurological*: increased risk of seizures. *Ophthalmological*: glaucoma. *Psychiatric*: psychosis and suicidal ideation.

Dexamethasone has a lower propensity to cause psychosis but is more likely to cause steroid myopathy and weakness due to its fluorinated chemical composition. IV administration of dexamethasone is associated with perineal paraesthesia, beginning within seconds of dose commencement and clearing soon after stopping. This is thought to be a chemical effect of the CS phosphate ester and can be avoided by administering the drug in a more dilute form or more slowly.

Contraindications

- *Absolute*: hypersensitivity and systemic infections (unless with concurrent anti-infective treatments).
- *Relative*: live virus vaccines (e.g. measles, VZV). In hepatic and renal impairment, caution is advised with the use of CS, due to the increased risk of fluid retention in these patients.

Use in special populations

- *Elderly*: age-related impairment of renal and hepatic function is commoner in the elderly. In addition, side effects, including osteoporosis, hypertension, hypokalaemia, diabetes, skin thinning, and infection, may be more severe in the elderly. These patients require frequent monitoring for complications, and lower dosing may be necessary.
- *Pregnancy*: there is weak evidence of an increased risk of cleft palate or lip in the foetus with maternal CS use, and prolonged use may lead to intrauterine growth retardation. CS have a very low teratogenic potential but may cause transient adrenal suppression in the neonate. Generally, however, the risks of CS use in pregnancy are far outweighed by the benefits to the mother, especially in active inflammatory or immune-mediated diseases.
- *Lactation*: prednisolone is excreted into breast milk. Although doses of <40 mg/day are unlikely to cause systemic effects in the infant, it is recommended that adjustments are made to the dosing interval to allow 4 h before breastfeeding.

Efficacy

1. *Methylprednisolone and prednisolone* are used to treat a large number of autoimmune and inflammatory conditions. For a list of uses, see p. 306. For a discussion of the evidence base for its use in these indications, see the individual conditions.
2. Dexamethasone.

- *Acute bacterial meningitis*: dexamethasone reduces the risk of severe hearing loss and short-term neurologic sequelae in bacterial meningitis by 33% and 17%, respectively. It does not affect overall mortality, but subgroup analysis has shown that it reduces mortality in meningitis caused by *S. pneumoniae* (RR 0.84, 95% CI 0.72–0.98). It is associated with an increase in recurrent fever, but not in other adverse events.
- *Cerebral oedema associated with malignancy*: there is a paucity of high-quality evidence showing that dexamethasone improves prognosis in cerebral oedema associated with malignancy. Nonetheless, up to 75% of patients treated with dexamethasone show neurological improvement at 48 h, and practical guidelines provide low-level recommendations of use, based on symptom severity. The practice is now widespread.

Dosing and monitoring

Dosing

1. *Dexamethasone*

- *Bacterial meningitis*: start treatment before or with the first antibiotic dose: 0.15 mg/kg every 6 h for 4 days. This can be stopped earlier if an alternative organism to *S. pneumoniae* is identified.
- *Cerebral oedema*: the dosage of dexamethasone used in the management of brain tumour-related cerebral oedema depends upon the speed of onset and severity of symptoms. In the acute, unstable situation, dexamethasone can be given by IV injection at 8–16 mg;

then 5 mg may be given by IM or IV injection 6-hourly thereafter for 2–4 days, prior to taper. In a more stable situation with a slow onset of symptoms, dexamethasone can be given by oral tablets in doses of 2–6 mg bd to qds, with or without a higher loading dose of 4–16 mg, depending on symptom severity. Dexamethasone should be withdrawn as rapidly as feasible, although in some patients with widespread cerebral oedema or particularly aggressive tumours, a slower taper may be required. In patients with good performance status, then taper by 50% every 4 days, aiming to complete withdrawal in 2–3 weeks. In those with a worse clinical condition, then taper more slowly, e.g. reduction by 25% every 7–8 days, and a low level of maintenance dexamethasone may be required to prevent the return of symptoms.

2. *Methylprednisolone*

- A wide range of dosing regimens can be used. Three days of daily IV doses of 1000 mg methylprednisolone or 5 days of daily PO doses of 500 mg methylprednisolone are commonly used for acute exacerbations of MS and other acute inflammatory conditions. In the context of an acute MS relapse some clinicians employ a short taper of prednisolone, following IV methylprednisolone, although there is no evidence base to support this practice.

3. *Prednisolone*

- See individual conditions for the usual dose. The general principles are that prednisolone can be started at high doses of 1 mg/kg od(a maximum dose of 60 mg is recommended for most conditions). MG is a notable exception to this regimen where a low dose on alternate days is gradually titrated upwards to avoid the 'steroid dip' in symptoms seen 4–10 days after starting high doses. Such high doses can be used in the longer term in some conditions but are usually tapered after the first week or month. This typically involves dose reductions of 10 mg/week, until a daily dose of 30 mg is reached. Reductions of 2.5 mg can then be made every 1–2 weeks, until a daily dose of 10 mg is reached, after which 1 mg decrements may be needed. This taper may need to be titrated to symptoms, and slower decrements of 1 mg/month may be initially needed in certain conditions such as neurosarcoidosis.

Monitoring

Patients should be monitored for the development of common side effects noted above, with provisions made to reduce the total steroid dose as soon as possible with steroid-sparing anti-inflammatory medications. In patients on high-dose steroids, consideration should be given to the co-prescription of medications for bone and gastric protection. If GCs have been administered for <3 weeks, treatment can be ceased without tapering. Tapering doses of GCs are required for longer, higher-dose (>40 mg/day prednisolone), or repeated treatment courses or in patients who may have adrenal suppression from another cause.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.24.
Interactions See Table 23.25.

Table 23.24 Pharmacokinetics of corticosteroids

	Hydrocortisone	Prednisolone	Methylprednisolone	Dexamethasone
Main routes of administration	IV, PO	PO	IV, PO	IV, PO
Onset of action (h)	IV: immediate; PO: 1–2	Unknown	IV: immediate; PO: 1–6	IV: 1; PO: unknown
Duration of action (h)	8–12	12–36	12–36	36–72
Oral bioavailability	96%	99%	88%	76%
T_{max} (h)	1.2	1.3	0.8	1.5
Protein binding	92%	86%	79%	77%
Metabolism	Hepatic glucuronidation and sulphate conjugation			
Excretion	Renal (<20% as unchanged drug)			
Elimination half-life (min)	80–115	150–210	78–188	190

IV, intravenous; PO, oral.

Table 23.25 Interactions of corticosteroids (CS)

Medications which alter CS plasma levels	Medications whose plasma levels are altered by CS	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenobarbital, phenytoin, rifampicin, primidone **Levels increased:** aprepitant (MP), asparaginase (dex), ciclosporin, diltiazem (MP), erythromycin, itraconazole, ketoconazole, oral contraceptives containing oestrogen, ritonavir, and related protease inhibitors	**Levels decreased:** aspirin, axitinib (dex), aquinavir (dex), calcium salts, caspofungin (dex), cobicistat (dex), elvitegravir (dex), indinavir (dex), isoniazid, lopinavir (dex), phenytoin (dex), rilpivirine (dex), sodium benzoate, sodium phenylbutyrate, telaprevir (dex), ticagrelor (dex), triazolam (dex) **Levels increased:** ciclosporin, phenytoin (dex)	**With antihyperglycaemics, antihypertensives, and pancuronium/vecuronium:** antagonizes hypotensive, hypoglycaemic, and muscle relaxant effects **With aspirin and NSAIDs:** increased risk of gastrointestinal bleeding **With drugs causing hypokalaemia, e.g. diuretics, β-agonists:** increased risk of hypokalaemia **With warfarin:** increased anticoagulant effect **With mifepristone:** reduced CS effect **With aldesleukin and mifamurtide:** reduced antineoplastic effect

(*Continued*)

Table 23.25 (*Contd.*)

Medications which alter CS plasma levels	Medications whose plasma levels are altered by CS	Pharmacodynamic interactions
		Dexamethasone with lenalidomide/thalidomide: increases thrombogenic effects when used in combination as chemotherapy for multiple myeloma

dex, dexamethasone; MP, methylprednisolone.

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Dimethyl and diroximel fumarate

Dimethyl and diroximel fumarate are both oral fumaric acid esters used in the management of relapsing-remitting multiple sclerosis (RRMS). Dimethyl fumarate was first licensed for the treatment of RRMS in 2014, in the UK. Gastrointestinal side effects are a common adverse effect with dimethyl fumarate. Diroximel fumarate is a second-generation drug, which demonstrates better tolerability. Dimethyl fumarate was first approved in 2013 by the FDA and licensed for use in 2014 in the UK. The FDA first approved diroximel fumarate in 2019, and it was licensed for use, in the UK, in 2022.

Uses

Licensed uses

In the UK

- *MS*: dimethyl and diroximel fumarate are licensed for the treatment of RRMS. Dimethyl fumarate is licensed for individuals aged 13 years and older, whilst diroximel fumarate is licensed for individuals aged 18 years and older.
- *In the USA*
- *MS*: dimethyl and diroximel fumarate are licensed for the treatment of relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary progressive disease in individuals aged 18 years and older.

Off-label uses

- None.

Mechanism of action

Dimethyl and diroximel fumarate are fumaric acid esters that have been shown to activate the nuclear factor (erythroid-derived 2)-like 2 or Nrf2 pathway, a pathway involved in the cellular response to oxidative stress, but the exact mechanism of action of this drug is unclear. Studies in MS and prior to this, in the management of psoriasis, have demonstrated immunomodulatory properties, including a reduction in TH1 and TH17 cytokine profiles, and reduced circulating levels of lymphocytes.

Both medications are prodrugs and are rapidly hydrolysed in the gastrointestinal tract. Dimethyl fumarate is cleaved into monomethyl fumarate and methanol, whilst diroximel fumarate is cleaved into monomethyl fumarate and 2-hydroxyethyl succinimide, an inactive metabolite. Monomethyl fumarate is the primary active metabolite of both prodrugs, hence the clinically beneficial effects of both drugs are assumed to be similar. Methanol is thought to irritate the gut resulting in gastrointestinal side effects; this is thought to be why diroximel fumarate is better tolerated than dimethyl fumarate.

Toxicity and side effects

- *Common—Dermatological*: erythema, flushing (in a third, severe enough to require discontinuation in 3% of patients taking dimethyl fumarate—aspirin 75 mg before taking the medication may help), pruritus, and rash. *Gastrointestinal*: abdominal pain, deranged LFTs, diarrhoea, dyspepsia, gastritis, gastroenteritis, nausea, and vomiting (GI symptoms often settle and can be minimized by eating fat and protein-rich foods before taking the medication). *Genitourinary*: ketonuria and proteinuria. *Haematological*: lymphopenia ($<0.5 \times 10^9$/L in 6%—these patients are probably at higher risk of progressive multifocal leukoencephalopathy (PML)). *Neurological*: paraesthesiae.
- *Serious—Dermatological*: generalized erythema. *Immunological:* anaphylaxis and angioedema. *Neurological:* PML is rare, but has been described although for the most part in patients with low lymphocyte counts, particularly low CD8+ T cells.
- In a head-to-head study of dimethyl fumarate (DMF) compared to diroximel fumarate (DRF) in patients with RRMS. 32.8% of patients treated with DRF developed flushing compared to 40.6% with DMF, and 15.4% of patients treated with DRF developed diarrhoea compared to 22.3% with DMF. The degree of flushing and diarrhoea was less severe in the DRF group than the DMF group, as evidenced by the fact that 0.8% of patients in the DRF group and 4.8% of patients in the DMF group discontinued the study due to gastrointestinal side effects.

Contraindications

- *Absolute*: known hypersensitivity to dimethyl or diroximel fumarate, and suspected or confirmed progressive multifocal leukoencephalopathy.

Diroximel fumarate is not recommended in patients with moderate or severe renal impairment (GFR <60 mL/min).

- *Relative*: dimethyl fumarate has not been studied in renal or hepatic impairment; but given its main routes of metabolism, no dose adjustments are routinely recommended. Diroximel fumarate does not need to be reduced in hepatic impairment.

Use in special populations

- *Elderly*: these drugs have not been studied in the elderly. In general, the elderly are more likely to have age-related hepatic and renal impairment and may be more likely to suffer from side effects.
- *Pregnancy*: there is insufficient data from human studies. Rodent studies have shown teratogenicity at doses lower than the recommended human dose. These drugs are not recommended during pregnancy and should only be used if potential benefits clearly outweigh the risks to the foetus.
- *Lactation*: there is little human data on effects on an infant if these drugs are taken by the mother whilst breastfeeding. The amount of active metabolite in breast milk is low. Given the lack of data, it may be better to avoid breastfeeding. If it is used, then infants should be monitored for flushing and diarrhoea.

Efficacy

Dimethyl fumarate:

RRMS: For the licensed 240 mg bd dose, both the DEFINE (a dose comparison RCT investigating dimethyl fumarate vs. placebo) and CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis—an RCT investigating dimethyl fumarate vs. glatiramer) studies demonstrated a significant reduction in the proportion of patients relapsing at 2 years. The reduction in absolute risk reduction (ARR) was 53% (DEFINE) and 44% (CONFIRM) vs. placebo. In comparison, glatiramer acetate reduced the ARR by 29%.

The risk of confirmed EDSS progression sustained for 3 months at 2 years was reduced by 38% ($p = 0.005$) in DEFINE and by 21% ($p = 0.25$, not significant) in CONFIRM, compared with placebo. In addition, the inflammatory activity on MRI was significantly reduced in both studies, with >70% reduction in T2 and gadolinium-enhancing lesions and >57% reduction in T1 lesions ($p < 0.0001$ for all values) in both studies, compared with placebo.

Diroximel fumarate:

RRMS: Given the active metabolite is the same for both dimethyl fumarate and diroximel fumarate, approval was based on historical data from dimethyl fumarate rather than a new phase 3 randomized controlled trial in RRMS. The differences in gastrointestinal side effects between the two medications have been compared in two phase 3 studies. The results of the head-to-head study are detailed in the toxicity and side effects section (see earlier).

Dosing and monitoring

Dosing

Dimethyl fumarate: Start treatment at 120 mg bd, with food. Increase to a usual maintenance dose of 240 mg bd at 7 days.
Diroximel fumarate: Start treatment at 231 mg bd. Increase to a usual maintenance dose of 462 mg bd at 7 days.

Monitoring

An FBC should be checked prior to initiation and then thrice monthly, if lymphocytes drop to very low levels for more than 6 months then consider stopping. A baseline MRI should be performed within 3 months of starting treatment to be used as a reference in case symptoms suggestive of PML arise. Renal and liver function should be assessed prior to treatment initiation and then every 6–12 months as clinically indicated.

Pharmacokinetics and interactions

Pharmacokinetics

These drugs undergo rapid pre-systemic hydrolysis by esterases in the gastrointestinal tract following oral administration. This converts the drug to the active monomethyl fumarate. Maximal plasma concentrations of monomethyl fumarate are reached at 2–2.5 h for DMF and 2.5–3 h for DRF. A high-fat, high-calorie meal delays absorption of both medications but does not affect the total amount of medication absorbed. 27–45% of monomethyl fumarate is plasma protein bound.

The active metabolite, monomethyl fumarate, is metabolized by the tricarboxylic acid cycle and primarily eliminated by expiration as carbon dioxide. Hepatic and renal excretion account for 0.9% and 15.5% of elimination, respectively. The terminal half-life of monomethyl fumarate is ~1 h.

Interactions

Intake with significant amounts of alcohol may increase the risk of gastrointestinal side effects. Dimethyl and diroximel fumarate should not be administered together.

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Dopamine agonists

Dopamine agonists (DA) were first introduced as a treatment for PD in the 1970s. Bromocriptine was synthesized in 1965, and other ergot-based DAs soon followed (cabergoline, pergolide, and lisuride). Due to the risk of fibrosis (retroperitoneal, cardiac, and pulmonary), ergot-based DAs are now only rarely used in the treatment of PD. Non-ergot DAs (apomorphine, pramipexole, ropinirole, and rotigotine) are preferred, due to their safer side effect profile. Given their readily available successors, we have not discussed the ergot-based DA further in this drug monograph.

DAs are most commonly used in early Parkinson's disease (PD), in order to minimize motor complications seen with levodopa use. They are also preferred to levodopa in the management of RLS, as there is a lower chance of augmentation. Pramipexole and ropinirole are available in oral formulations, whilst rotigotine is available as a transdermal patch, and apomorphine as a sublingual and SC infusion/injection.

Uses

Licensed uses

In the UK/USA

- *PD*.
  1. *Apomorphine* is licensed for acute, intermittent treatment of 'on–off' phenomena in PD not adequately controlled by oral medication in individuals aged 18 years and older. Sublingual and SC infusion/injection formulations are available in the US. Acute SC injection and continuous SC infusions are available in the UK. SC infusion is indicated if motor control is unsatisfactory with intermittent injections or, if there are ≥10 sudden off periods in a day
  2. *Pramipexole* is licensed for the treatment of PD as a monotherapy or as an adjunct to levodopa throughout the course of the disease in individuals aged 18 years and older.
  3. *Ropinirole* is licensed for the treatment of PD as a monotherapy or as an adjunct to levodopa throughout the course of the disease in individuals aged 18 years and older.
  4. *Rotigotine* is licensed for the treatment of PD as a monotherapy in early disease or as an adjunct to levodopa over the course of the disease when the effect of levodopa becomes less consistent in individuals aged 18 years and older.
- *RLS*.
  1. *Pramipexole* is licensed for the treatment of moderate-to-severe RLS in individuals aged 18 years and older.
  2. *Ropinirole* (standard tablet) is licensed for the treatment of moderate-to-severe primary RLS in individuals aged 18 years and older.
  3. *Rotigotine* is licensed for the treatment of moderate-to-severe primary RLS in individuals aged 18 years and older.

Off-label uses

- None.

Mechanism of action

Whilst the precise mechanism of action is unknown, the antiparkinsonian effects of the non-ergoline-derived DAs are thought to be due to action at primarily central post-synaptic D2 dopamine receptors within the striatum. This is also thought to be the mode of action when treating RLS. Due to the action at presynaptic D2 receptors, which inhibit the release of dopamine, there may be an initial deterioration in PD symptoms.

Toxicity and side effects

- *Common—Cardiovascular*: orthostatic hypotension, peripheral oedema, and syncope. *Gastrointestinal*: constipation, nausea, and vomiting. *Immunological:* oral soft tissue swelling and urticaria (sublingual apomorphine). *Neurological*: dizziness, dyskinesias, fatigue, hallucinations, headache, insomnia, sleep disorder, and somnolence (may be sudden onset).
- *Serious—Cardiovascular*: atrial fibrillation (AF), chest pain, long QT syndrome, and tachycardia. *Haematological*: haemolytic anaemia has been reported with apomorphine. *Musculoskeletal*: rhabdomyolysis (only pramipexole). *Psychiatric*: aggression, agitation, DAWS, ICDs, paranoia, and psychosis.

Contraindications

- *Absolute*: hypersensitivity to a drug or any of its excipients. Apomorphine should not be used in patients with respiratory depression, dementia, psychotic diseases, and hepatic insufficiency, in patients whose 'on' response to levodopa has significant dyskinesia/dystonia, or alongside 5HT3 antagonists (e.g. ondansetron), as this may lead to significant hypotension. Alcohol should be avoided while on apomorphine. The rotigotine patch should be removed prior to MRI and cardioversion, as it contains aluminium. Ropinirole should not be used if the creatinine clearance (CrCl) is <30 mL/min without dialysis (no dose adjustment is required in mild-to-moderate renal impairment). The ropinirole prolonged-release tablet should not be used in any degree of hepatic impairment, and the standard-release tablet should not be used in severe hepatic impairment.
- *Relative*: for apomorphine, reduce the test dose and starting dose to 1 mg in moderate-to-severe renal impairment. Cardiovascular disease, patients at risk of long QT syndrome, and neuropsychiatric illness are relative contraindications for apomorphine, pramipexole, ropinirole, and rotigotine.

Pramipexole dose should be used with caution in dialysis patients and lowered in those with renal dysfunction, as this is the primary route of elimination. CrCl 20–50 mL/min: initiate at 0.088 mg base (0.125 mg salt) bd, and increase to a maximum daily dose of 1.57 mg base (2.25 mg salt). CrCl <20 mL/min: initiate at 0.088 mg base (0.125 mg salt) od, and increase to maximum daily dose of 1.1 mg base (1.5 mg salt). Pramipexole dose does not need to be adjusted in hepatic impairment.

Rotigotine does not require dose adjustment in renal impairment but should only be used with caution in patients with severe hepatic impairment.

Use in special populations

- *Elderly*: no dose alteration is routinely required; however, extra caution should be taken when first starting treatment (particularly apomorphine), as the elderly are at increased risk of postural hypotension and falls.
- *Pregnancy*: no safety data exist from human studies. No teratogenicity has been noted in animal studies, although some DAs have been shown to be embryotoxic. Use of these drugs should be avoided, unless the benefits outweigh risks.
- *Lactation*: data on the excretion of these medications into breast milk is not known for most of these agents; DAs may reduce lactation; hence manufacturers advise against use by nursing mothers.

Efficacy

- *Apomorphine*: several double-blind studies have evaluated the efficacy of SC apomorphine in providing rescue from 'off' episodes in patients with advanced PD. *APO202*, a double-blind, placebo-controlled study, evaluated the efficacy of apomorphine ($n = 18$) administered, as needed, as rescue therapy from spontaneous 'off' episodes in patients with advanced PD who were experiencing >2 h 'off' time per day, despite optimal oral therapy. ~95% of 'off' episodes per patient were successfully treated, compared with 23% with placebo ($p < 0.001$). Sublingual apomorphine efficacy was established in one double-blind, randomized, placebo-controlled, parallel-group study ($n = 109$) where the treatment group showed a least-square mean change from predose MDS-UPDRS part 3 score of –11.1 points vs. –3.5 points for the placebo group ($p = 0.0002$).
- *Pramipexole*: a 12-week randomized, double-blind, placebo-controlled trial of pramipexole in early PD ($n = 311$) found a significant reduction in UPDRS at all doses, compared to placebo, of 4.4–4.7 points, depending on the dose used ($p < 0.0001$ for each comparison to placebo). Quality of life, as measured by Parkinson's disease questionnaire-39 (PDQ-39), was significantly improved in the 0.75 mg bd and 0.5 mg tds groups ($p < 0.05$), but not in the 0.5 mg bd group. Long-term efficacy and tolerability of pramipexole were confirmed in a 57-month open-label extension of a double-blind RCT ($n = 262$).
- *Ropinirole*: a double-blind RCT evaluated the effect of ropinirole (0.75–24 mg/day), sumanirole (a highly selective D2 agonist not approved for medical use, 1–16 mg/day), and placebo over 40 weeks in patients with PD ($n = 614$). There were significant improvements in UPDRS from baseline (−5.2), compared to worsening with placebo (0.38). The main adverse events were somnolence and nausea.
- *Rotigotine*: a randomized, double-blind, controlled trial compared the effect of rotigotine (8 mg/day), ropinirole (24 mg/day), and placebo on patients with early PD ($n = 561$). Rotigotine was significantly more effective than placebo, with a reduction of 52% vs. 30% with placebo, in UPDRS scores ($p < 0.0001$). Rotigotine was not inferior to ropinirole; however, the study was not sufficiently powered to differentiate which medication was more effective.

Dosing and monitoring

Dosing

- Apomorphine.
    - *PD: SC injection*: the 'threshold dose' needs to be established before treatment can begin. Other PD medications should be first withheld to establish this dose. To prevent nausea and vomiting, patients should be pre-treated with domperidone 20 mg tds for 3 days, and testing should be performed in a specialist clinic. Start treatment at 1 mg and assess response at 30 min. Increase the dose by 1 mg and continue to assess the level of response and tolerability. The effective dose will result in >20% improvement in UPDRS score. The manufacturer advises that the total daily dose should not exceed 100 mg and that individual bolus injections should not exceed 10 mg. When the threshold dose is established, it can be administered SC at the first signs of an off period. Patients should be observed for 1 h after to assess response to treatment. *Continuous SC infusion*: start treatment at 1 mg/h. Increase the dose by 0.5 mg/h every 4 h, up to a maximum of 4 mg/h, depending on clinical response. The infusion should be stopped overnight to prevent tolerance from developing. The infusion site should be changed 12-hourly. The dose of levodopa and other dopaminergic agents required may be reduced. *Sublingual:* start the initial dose at 10 mg and assess response. The maximum single dose is 30 mg and should not be administered more than 5 times a day.
- *Pramipexole*.
    - *PD*: start treatment at subtherapeutic levels to avoid intolerable adverse effects, 0.088 mg base (0.125 mg salt) tds. The dose can be increased after 1 week to 0.18 mg base (0.25 mg salt) tds, and then to 0.35 mg base (0.5 mg salt) tds after another week. The maximum daily dosage is 3.3 mg base (4.5 mg salt). Dose escalation should balance symptom improvement with the onset of side effects.
    - *RLS*: start treatment at 0.088 mg base od, and increase, according to symptoms and tolerability, to a maximum dose of 0.54 mg base od.
- *Ropinirole*.
    - *PD*: increase by 0.25 mg tds each week to 1 mg tds over 4 weeks. This is usually presented as a 'starter pack'. Following this, larger increases in dose can be made. A 'follow-on' pack is available which increases the daily dose from 1 mg to 3 mg tds over 4 weeks, as tolerated. Maximum dose is 24 mg/day. Prolonged-release tablets allow for od dosing. Start treatment at 2 mg od for the first week; this can be increased every 2 weeks by 2 mg, until adequate symptom control is reached. Maximum dose 24 mg/day. Levodopa dose may be reduced when DAs are used as adjuncts.
    - *RLS*: start treatment at 0.25 mg od 1–3 h prior to sleep. If tolerated, this can be increased to 0.5 mg after 2 days, then to 1 mg after a further 5 days, then by 0.5 mg every week up to a usual maintenance dose of 2 mg od. A maximum dose of 4 mg od can be used, if required.
- *Rotigotine*.
    - *PD*: start treatment at 2 mg/24 h (advanced PD: 4 mg/24 h) and increase weekly by 2 mg/24 h. The usual treatment dose is 6–16 mg/24 h.

- *RLS*: start treatment at 1 mg/24 h. Increase weekly by 1 mg/24 h. The maximum recommended dose is 3 mg/24 h.

Monitoring

- Treatment withdrawal: gradual dose reduction should occur to minimize the risk of NMS and DAWS.
- With apomorphine: FBC, renal, hepatic, and cardiovascular function (QT interval) should be monitored at baseline and 6-monthly thereafter.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.26.
Interactions See Table 23.27.

Table 23.26 Pharmacokinetics of non-ergot-based DAs

	Apomorphine	Pramipexole	Ropinirole	Rotigotine
Main routes of administration	SC	PO	PO	Patch
Oral bioavailability	100%	90–100%	50%	Variable
T_{max}	10 min	2 h	1–2 hER: 6–10 h	15–18 h
Protein binding	85–90%	15%	40%	90%
Metabolism	NA	Negligible (<10%)	Hepatic CYP1A2, CYP3A4	Hepatic CYP isoenzymes
Pharmacologically active metabolites	NA	No	No	No
Elimination half-life	40 min	8.5 h	6 h	5–7 h

ER, extended release; NA, information not available; PO, oral; SC, subcutaneous.

Table 23.27 Interactions of non-ergot-based DAs

Medications which alter non-ergot-based DA plasma levels	Pharmacodynamic interactions
1. Pramipexole Levels increased: drugs which inhibit secretory transport at the renal tubules, e.g. cimetidine 2. Ropinirole Levels decreased: CYP1A2 inducers, e.g. cyproterone Levels increased: high-dose oestrogens and CYP1A2 inhibitors	With antidopaminergic agents, e.g. antipsychotics: can antagonize the effect of DAs With antihypertensives: increased risk of hypotension Apomorphine, with agents known to prolong QTc, e.g. macrolide antibiotics: may increase QTc interval

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Factor Xa inhibitors

Factor Xa inhibitors are a group of anticoagulants that act by blocking the activity of Factor Xa. This prevents the conversion of prothrombin to thrombin, and hence reduces clot formation. Apixaban, edoxaban, and rivaroxaban are the three most commonly used in neurological practice. Rivaroxaban was the first agent to receive market approval, and was first used in the UK in 2008; it was followed by apixaban in 2011 and edoxaban in 2015. Apixaban and rivaroxaban have a licensed reversal agent; andexanet alfa. Andexanet alfa has been used in the reversal of edoxaban, although this is off-label.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: apixaban is licensed for the prophylaxis of stroke and systemic embolism in patients with non-valvular AF (NVAF) in individuals aged 18 years and older. In the UK, patients need to score at least 1 point on the CHADS2 VASc score.

Off-label uses

- None.

Mechanism of action

Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade, inhibiting both thrombin formation and the development of thrombi.

Toxicity and side effects

- *Common—Cardiovascular*: hypotension. *Dermatological*: pruritus, rash. *Gastrointestinal*: abdominal pain, abnormal liver function tests, constipation, diarrhoea, dyspepsia, nausea, vomiting. *Haematological*: anaemia. *Musculoskeletal*: pain in extremities. *Neurological*: headaches.
- *Serious—Haematological*: haemorrhage. *Immunological*: allergic reaction. *Neurological*: intracranial haemorrhage.

Contraindications

- *Absolute*: Hypersensitivity to the medication or its excipients. Severe hepatic impairment and active significant bleeding. End-stage renal failure: CrCl <15 mL/min.
- *Relative*: Conditions associated with an increased risk of bleeding, e.g. peptic ulcer disease. Reduce the apixaban dose to 2.5 mg twice daily in patients with CrCl 15–30 mL/min, the edoxaban dose to 30 mg once daily in patients with CrCl 15–50 mL/min and the rivaroxaban dose to 15 mg once daily in patients with CrCl 15–50 mL/min.

Use in special populations

- *Elderly*: No dose adjustment is necessary in the elderly population for edoxaban and rivaroxaban. See dose adjustment in the >80 years age group, under dosing, for apixaban. The elderly population experience an age-related decline in renal and hepatic function; hence these parameters should be regularly monitored during treatment.
- *Pregnancy*: Toxicity has been demonstrated in animal studies involving edoxaban and rivaroxaban, but not apixaban. Safety and efficacy have not been established in human pregnancy. There is an increased risk of venous thromboembolism during pregnancy, which should be weighed against the risk of pregnancy-related haemorrhage, reproductive toxicity, and emergent delivery-related haemorrhage. In general, Factor Xa inhibitors should be avoided in pregnancy, and an alternative anticoagulant is preferred.
- *Lactation*: Rivaroxaban is present in human breastmilk, but at levels lower than that considered necessary to have an anticoagulant effect, and hence could potentially be used by nursing mothers if other options are not available. If rivaroxaban is used, the infant should be monitored for signs of bleeding and bruising. Apixaban is present at high levels in breastmilk, and it is unclear if edoxaban is present in breastmilk, hence an alternative anticoagulant or method of feeding should be used if these two medications are under consideration.

Efficacy

Apixaban: In the *ARISTOTLE* trial, 18,201 AF patients with intermediate risk of clinical thromboembolic stroke (mean CHADS2 score of 2.1) were randomly assigned to either apixaban (5 mg bd) or warfarin (target INR 2.0–3.0). The primary composite endpoint of stroke and systemic embolism was significantly reduced (0.33% per year) in the apixaban group (hazard ratio 0.79 (95% CI 0.66–0.95; p <0.001 for non-inferiority and p = 0.01 for superiority)). In the *AVERROES* trial, 5,599 patients with AF who were not candidates for warfarin therapy were randomized to either apixaban (5 mg bd) or aspirin (81–324 mg daily) to assess if apixaban was superior to aspirin for preventing stroke or systemic embolism. The study was stopped early at interim analysis due to a significant reduction in stroke and systemic embolism with apixaban (hazard ratio 0.45 (95% CI 0.32–0.62; p <0.0001)).***Edoxaban:*** For NVAF, Edoxaban was studied in a multinational, double-blind, non-inferiority study comparing the efficacy and safety of two edoxaban treatment arms (60 mg and 30 mg) to warfarin (titrated to INR 2.0–3.0). The primary endpoints were the incidence of stroke and systemic embolic events in patients with NVAF. The annualized rate of the primary endpoint during treatment was 1.5% with warfarin as compared with 1.18% with high-dose edoxaban (p <0.001 for non-inferiority) and 1.61% with low-dose edoxaban (p = 0.005 for non-inferiority).

Rivaroxaban: In a double-blind RCT (ROCKET AF), rivaroxaban was shown to be non-inferior to warfarin for the primary endpoint of stroke or systemic embolism in patients with NVAF who were at moderate to high risk of stroke (hazard ratio 0.88; 95% CI 0.74–1.03; p <0.001). Intracranial and fatal bleeding was significantly less frequent in the rivaroxaban group (0.5% vs. 0.7%, p = 0.02 for intracranial, and 0.2% vs. 0.5%, p = 0.03 for fatal bleeding for rivaroxaban vs. warfarin).

Dosing and monitoring

Dosing

For non-valvular AF *(note dose adjustments are recommended in renal impairment—see above):*

Apixaban: The recommended dose is 5 mg twice daily. Halve the dose to 2.5 mg twice daily if two or more of the following factors are present: age >80 years, body weight <60 kg, or serum creatinine ≥133 micromol/L.

Edoxaban: The recommended daily dose is 60 mg once daily.

Rivaroxaban: The recommended daily dose is 20 mg once daily.

Monitoring

There is no need for monitoring of coagulation parameters during treatment with Factor Xa inhibitors in routine clinical practice. However, if clinically indicated, anti-Xa assay may be useful in exceptional situations where knowledge of Factor Xa exposure may help to inform clinical decisions, e.g. overdose and emergency surgery.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.28.

Interactions See Table 23.29.

Table 23.28 Pharmacokinetics of Factor Xa inhibitors

	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	50%	62%	80–100%
T_{max}	3–4 h	1–2 h	2–4 h
Protein binding	87%	55%	92–95%
Metabolism	Hepatic: predominantly CYP3A4.	Minimal. Oxidation by CYP3A4 and hydrolysis by plasma esterases	Hepatic: CYP3A4, CYP2J, and CYP independent mechanisms
Pharmacologically active metabolites	No	No	No
Elimination half-life	12 h	10–14 h	5–9 h (11–13 h in elderly)
Excretion	Primarily faeces	Mixed faeces and urine	Primarily urine

Table 23.29 Interactions of Factor Xa inhibitors

Medications which alter Factor Xa medications plasma levels	Medications whose plasma levels are altered by Factor Xa medications	Pharmacodynamic interactions
All Factor Xa inhibitors Levels decreased: P-gp inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's Wort) Levels increased: P-gp inhibitors (e.g. amiodarone, cyclosporine, erythromycin ketoconazole, quinidine, verapamil).	Edoxaban: Levels decreased: Verapamil. Levels increased: Digoxin.	With anticoagulants, antiplatelets and NSAIDs: increased risk of bleeding.

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Gepants

The gepants are a group of CGRP receptor antagonists used for the treatment of migraine. Currently available medications include atogepant, rimegepant, ubrogepant, and zavegepant. Atogepant and ubrogepant are available as standard oral tablets, rimegepant is available as an orally disintegrating tablet and zavegepant is available as a nasal spray. Ubrogepant and zavegepant are licensed for the acute treatment of migraine. Atogepant is licensed as a preventative treatment for episodic migraine, and rimegepant is licensed as both an acute treatment for migraine and as a prophylactic for episodic migraine. Ubrogepant was the first gepant approved for use by the FDA in 2019. As of September 2023, all four agents are licensed in the USA, whilst only atogepant and rimegepant are approved for use in the UK. Recent systematic reviews have suggested that triptans may be more effective at delivering pain freedom at 2 h, but both triptans and ditans (lasmiditan) are associated with higher rates of side effects than gepants. A good response to triptans predicts a good response to gepants, but gepants can be effective even where triptans have failed and may be a safer option than triptans in patients with significant cardiovascular disease.

Uses

Licensed uses

In the UK/USA (Licensing is the same)
Atogepant: Atogepant is licensed for the preventative treatment of migraine in individuals aged 18 years and older.

Rimegepant: Rimegepant is licensed for the acute and preventative treatment of migraine in individuals aged 18 years and older.

In the USA

Ubrogepant/Zavegepant: Ubrogepant and zavegepant are licensed for the acute treatment of migraine in individuals aged 18 years and older.

Off-label uses

- Cluster headache and trigeminal neuralgia.

Mechanism of action

The gepants are CGRP receptor antagonists. CGRP is released by the activated trigeminovascular system during migraine and is a potent vasodilator. CGRP infusion will trigger a migraine attack in migraineurs and blockade of the CGRP receptor reduces the severity and duration of pain associated with migraine.

Toxicity and side effects

- *Common—Dermatological:* Rash. *Gastrointestinal:* Constipation or diarrhoea. *Neurological:* fatigue and somnolence.
- *Serious—Dermatological*: Hypersensitivity reactions including angioedema (Rare).

Contraindications

- *Absolute*: hypersensitivity to the medication or its excipients. Ubrogepant should not be prescribed with strong CYP3A4 inducers, e.g. phenytoin, barbiturates, rifampin, and St John's wort). Avoid use of atogepant, rimegepant, and zavegepant in severe hepatic impairment. Avoid use of rimegepant and ubrogepant in severe renal impairment (CLcr<15 mL/min). Avoid use of zavegepant in moderate and severe renal impairment (CLcr<30 mL/min).
- *Relative*: In severe hepatic impairment, patients should not use more than 50 mg of ubrogepant within 2 h. The maximum daily dose of atogepant in patients with severe renal impairment (CLcr<15 mL/min) is 10 mg/day.

Use in special populations

- *Elderly*: no dose adjustments are routinely required in the elderly population, although in general it would be reasonable to consider trialling lower doses in the first instance, given the increased likelihood of hepatic and renal impairment in this population.
- *Pregnancy*: there are no adequate data on the teratogenic risk of gepants in pregnant women. In animal studies, variations in organogenesis have been noted when gepants were administered, but only at doses several times the equivalent of the maximum recommended human dose. Use only if potential benefits outweigh risks.
- *Lactation*: there is no data on the use of gepants during breastfeeding. In rodent models, both atogepant and ubrogepant were present in breastmilk, at levels similar to or higher than maternal plasma levels. These studies have not been undertaken for rimegepant or zavegepant. Given the lack of available data, an alternative medication or an alternative feeding method may be preferred.

Efficacy

Acute treatment of migraine

Rimegepant: Three phase 3 randomized controlled trials evaluated the efficacy of rimegepant for acute migraine therapy. The most recent trial was published in 2019. 75 mg of rimegepant resulted in pain freedom in 21% of people at 2 h (compared to 11% with placebo, $p < 0.0001$).

Ubrogepant: Two phase 3 randomized controlled trials evaluated the efficacy of ubrogepant for acute migraine therapy. The most recent trial was published in 2019. The rate of freedom from pain at 2 h was 11.8% with placebo, 19.2% with 50 mg ubrogepant and 21.2% with 100 mg of ubrogepant ($p = 0.002$ and $p < 0.0001$, respectively).

Zavegepant: A phase 2/3 dose-ranging clinical trial evaluated the efficacy of zavegepant for the acute treatment of migraine. The rate of freedom from pain at 2 h was 15.5% with placebo, 19.6% with 5 mg, 22.5% with 10 mg and 23.1% with 20 mg (this was a statistically significant improvement when compared to placebo; $p = 0.1214$, $p = 0.0113$, and $p = 0.0055$, respectively).

Preventative treatment of migraine

Atogepant: Two phase 3 randomized controlled trials evaluated the efficacy of atogepant as a preventative treatment for episodic migraine. All treatment doses resulted in a significant reduction in mean monthly migraine days compared to placebo. Patients in the placebo group had a reduction in migraine days of 2.9 days. Migraine days were reduced by 4 days with atogepant 10 mg od ($p = 0.024$), 3.8 days with atogepant 30 mg od ($p = 0.039$), 3.6 days with atogepant 60 mg od ($p = 0.039$), 4.2 days with atogepant 30 mg bd ($p=0.0034$) and 4.1 days with atogepant 60 mg bd ($p = 0.0031$).

Rimegepant: A single phase 2/3 randomized, double-blind, placebo-controlled trial evaluated the efficacy of rimegepant as a preventative treatment for episodic migraine. Patients in the placebo group had a reduction in migraine days of 3.5 days. The mean monthly migraine days were reduced by 4.3 days with 75 mg of rimegepant compared to 3.5 days with placebo ($p = 0.0099$).

Dosing and monitoring

Dosing

Acute treatment of migraine:

Rimegepant: Take 75 mg at the onset of migraine.

Ubrogepant: Take 50 or 100 mg at the onset of migraine. A further dose can be taken 2 h after the initial dose. The maximum recommended dose within 24 h is 200 mg. Use 50 mg per dose, and a maximum of 100 mg over 2 h in patients with severe hepatic or renal impairment (CLcr 15–29 mL/min), or who take weak CYP3A4 inhibitors, CBRP, and/or P-gp only inhibitors. The maximum recommended dose is 50 mg per 24 h in patients who take concomitant moderate CYP3A4 inhibitors.

Zavegepant: Take 10 mg as a single spray in one nostril at the onset of migraine.

Preventative treatment of migraine:

Atogepant: Take 60 mg once daily. Reduce dose to 10 mg in severe renal impairment and with strong CYP3A4 inhibitors. Consider reducing to 30 mg once daily if there is concomitant use of moderate and strong CYP3A4 inducers. Reduce dose to 10 or 30 mg once daily if there is concomitant use of OATP inhibitors.

Rimegepant: Take 75 mg every other day.

Monitoring

No routine monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.30.

Interactions See Table 23.31.

Table 23.30 Pharmacokinetics of gepants

	Atogepant	Rimegepant	Ubrogepant	Zavegepant
Main routes of administration	PO	PO	PO	IN
Bioavailability	NA	64%	NA	5%
T_{max}	1–2 h	~1.5 h	~1.5 h	30 min
Protein binding	~95%	~96%	~87%	90%
Metabolism	Hepatic, mainly CYP3A4	Hepatic, mainly CYP3A4> CYP2C9	Hepatic, mainly CYP3A4	Hepatic, mainly CYP3A4> CYP2D6
Elimination half-life	~11 h	~11 h	5–7 h	~6.55 h
Excretion	Mainly faeces (42% as unchanged drug)	Mainly faeces 78% (42% as unchanged drug)	Mainly faeces (42% as unchanged drug)	Mainly faeces (80% as unchanged drug)

NA, information not available; IN, intranasal; PO, oral.

Table 23.31 Interactions of gepants

Medications which alter plasma levels of mirabegron
Levels increased:
All gepants except zavegepant;
Strong CYP3A4 inhibitors, e.g. clarithromycin, itraconazole, and ketoconazole.
Moderate CYP3A4 inhibitors, e.g. cyclosporine, ciprofloxacin, and grapefruit juice.
Atogepant/zavegepant—Strong OATP inhibitors e.g. cyclosporine.
Rimegepant—Concomitant administration of P-gp or breast cancer resistance protein (BCRP inhibitors) may increase exposure to rimegepant, e.g. amiodarone, lansoprazole etc.
Levels decreased:
All gepants except zavegepant:
CYP3A4 inducers, e.g. carbamazepine, phenytoin, rifampicin, and St John's wort.
Zavegepant: Intranasal decongestants may lower the exposure to zavegepant.

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Glucosylceramide synthase inhibitors

Both eliglustat and miglustat are glucosylceramide synthase inhibitors that are licensed for use in Type 1 Gaucher's disease (GD). Miglustat was first licensed for us in 2002 in Europe. Eliglustat is a second-generation substrate replacement therapy (SRT) that was licensed in 2014 in Europe. They have both been shown to be effective in reducing the accumulation of glucosylceramide in GD and improving clinical symptoms. However, eliglustat is generally considered to be more effective than miglustat, and it has a significantly lower risk of gastrointestinal side effects.

Uses

Licensed uses

In the UK/USA

- *Gaucher disease:* Eliglustat and miglustat are licensed for the treatment of patients with Type 1 Gaucher disease, in individuals aged 18 years and older. Eliglustat is not licensed for use in patients who are CYP2D6 ultra-rapid metabolizers. Miglustat is only licensed for patients with mild-to-moderate disease, in the USA is specifically licensed for patients for whom ERT is not an option.
- *In the UK only*
- *Niemann-Pick type C:* Miglustat is licensed for the treatment of progressive neurological manifestations of patients with Niemann-Pick type C, in individuals aged 18 years and older.

Off-label uses

- Miglustat is used as an enzyme stabilizer of cipaglucosidase alfa ERT in individuals with Pompe disease.

Mechanism of action

Miglustat and eliglustat are both SRT for GD. They work by reducing the production of glucosylceramide, the glycosphingolipid that accumulates in GD. Miglustat is a glucose analogue, that acts as a competitive and reversible inhibitor of glucosylceramide synthase, the enzyme that catalyses the first step in the synthesis of glucosylceramide. By inhibiting glucosylceramide synthase, miglustat reduces the overall synthesis of glucosylceramide. Miglustat also inhibits disaccharidases with alpha-glycosidic linkages including sucrase, maltase, and isomaltase. This interferes with intestinal digestion of sucrose, maltose and isomaltose leading to an osmotic influx of water into the gastrointestinal tract, increased fermentation, and production of irritating metabolites. As a consequence, 85% of patients experienced diarrhoea in the clinical trials. In order to minimize this, this patient should fast for 2 h before and for 2 h after taking miglustat.

Eliglustat is a second-generation SRT. It is a ceramide analogue that competitively inhibits glucosylceramide synthase. In addition, eliglustat also inhibits other enzymes involved in glycosphingolipid synthesis, such as galactosylceramide synthase and sphingomyelin synthase. Given the absence of significant inhibition of disaccharidases with alpha-glycosidic linkages, only 10% of patients experienced diarrhoea in clinical trials.

Toxicity and side effects

- *Common—Cardiological*: Hypertension and palpitations (eliglustat). *Dermatological:* Hyperhidrosis, pruritis, rash, and urticaria. *Gastrointestinal*: Abdominal pain, constipation, diarrhoea, weight loss. *Musculoskeletal*: Arthralgia, muscle spasms, and myalgia. *Neurological*: Dysgeusia, headache and tremor (miglustat).
- *Serious—None*.

Contraindications

- *Absolute*:
- *Eliglustat and miglustat:* Hypersensitivity to the medication or its excipients.
- *Eliglustat*—eliglustat should not be used by patients who have galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption. Eliglustat causes mild increases in ECG intervals at significantly elevated plasma concentrations, hence the manufacturer advises avoiding using it in patients with cardiac disease, long QT syndrome, and in combination with Class IA and Class III antiarrhythmic agents. Eliglustat should not be used by patients who are CYP2D6 intermediate or extensive metabolizers and who take both moderate/strong CYP2D6 and CYP3A inhibitors, or who are CYP2D6 poor metabolizers who take a strong CYP3A inhibitor. Eliglustat is contraindicated in some patients with hepatic impairment depending on their CYP2D6 metabolism status. Prescribers are advised to read the product literature for further information.
- *Miglustat*: Miglustat is not recommended in patients with severe renal impairment (CrCl <30 mL/min/1.73 m^2).
- *Relative*: Eliglustat is not recommended in patients with renal impairment. There is little data with regards the use of miglustat in mild or moderate renal impairment and hence it should be used with caution in these patient groups.

Use in special populations

- *Elderly*: No dose adjustments are routinely recommended in the elderly population; however, the elderly population experiences an age-related decline in renal and hepatic function; hence, these parameters should be regularly monitored.
- *Pregnancy*: There are no data from human studies. Animal studies with miglustat have shown maternal and embryo-foetal toxicity, hence it is contraindicated in pregnancy. This has not been demonstrated for

eliglustat, but the manufacturer recommends avoiding its use during pregnancy as a precautionary measure.

- *Lactation*: There is no human data from human studies. Animal studies have demonstrated that eliglustat is present in mammalian milk. It is unclear if this is also the case for miglustat. Most would advise avoiding both of these medications during breastfeeding.

Efficacy

Eliglustat: Eliglustat has been shown to be effective in both patients with Type 1 Gaucher disease, who are treatment-naïve and those who previously received ERT. The phase 3 ENCORE study was a randomized, controlled, open-label non-inferiority trial in adults with Type 1 Gaucher disease ($n = 159$) that had reached therapeutic goals during the past 3 years on ERT. The study found that eliglustat was as effective (non-inferior) as ERT in reducing glucosylceramide levels, improving haematological parameters, and reducing visceral organ involvement. The ENGAGE study was a phase 3 randomized, double-blind, placebo-controlled trial ($n = 40$) which assessed changes in splenic volume in patients with GD treated with eliglustat (50 or 100 mg BD) or placebo. The study found significant improvements in splenic volume, haemoglobin level, liver volume, and platelet count in those treated with eliglustat compared to placebo.

Miglustat: Miglustat is an older substrate reduction therapy for Type 1 Gaucher disease. It is used second line if ERT has failed. It is effective in reducing the degree of hepato-splenomegaly, as well as lowering chitotriosidase levels; however, its efficacy in improving haematological parameters is limited.

Dosing and monitoring

Dosing

Eliglustat:

Dosing of eliglustat is based on CYP2D6 status. The dose for extensive and intermediate metabolizers is 84 mg orally twice daily and for poor metabolizers is 84 mg once daily.

Miglustat:

Gaucher disease type 1: The usual dose is 100 mg three times a day. If CrCl = 30–50 mL/min the dose is 100 mg once a day. The dose may be reduced to 100 mg once or twice a day if adverse effects develop.

Late-onset Pompe disease (used in combination with cipaglucosidase alfa): The dose is based on actual body weight: Weight ≥40 to <50 kg: 195 mg every other week. Weight ≥50 kg: 260 mg every other week.

Monitoring

Monitor FBC, coagulation parameters, electrolytes, chitotriosidase, angiotensin-converting enzyme (ACE), and tartrate-resistant acid phosphatase (TRAP) levels. MRI or CT scan (liver and spleen volume), skeletal X-rays, DXA; pulmonary function tests; ECG and echocardiography should be monitored at regular intervals to assess for complications and to monitor the efficacy of treatment.

Patients should have their CYP2D6 status assessed prior to commencing eliglustat.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.32.
Interactions See Table 23.33.

Table 23.32 Pharmacokinetics of glucosylceramide synthase inhibitors (GSIs)

	Eliglustat	Miglustat
Bioavailability	<5%	97%
T_{max}	1.5–6 h	2 h
Protein binding	76–83%	0%
Metabolism	Hepatic: CYP2D6>CYP3A4	Predominantly renally excreted as unchanged drug
Pharmacologically active metabolites	No	No
Elimination half-life	4–7 h (9 h in poor metabolizers)	6–7 h
Excretion	Primarily urine	Primarily urine

Table 23.33 Interactions of glucosylceramide synthase inhibitors

Medications which alter plasma levels of GSIs	Medications whose plasma levels are altered by GSIs
Eliglustat: Levels decreased: CYP3A inducers, e.g. carbamazepine, rifampicin, and phenytoin. Levels increased: CYP2D6 and CYP3A inhibitors, e.g. clarithromycin, fluoxetine, and ketoconazole. Miglustat: Enzyme replacement therapy with imiglucerase will reduce miglustat plasma levels	Eliglustat: Levels increased: CYP2D6 substrates, including tricyclic antidepressants and P-gp substrates, including colchicine and digoxin.

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Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are used as an adjunct in the management of Parkinson's disease (PD). They are typically used later in the disease course to treat motor fluctuations. Early MAOIs were non-selective in their action, inhibiting monoamine oxidase A (MAO-A) and B. Their inhibition of MAO-A, an isoenzyme responsible for tyramine, adrenaline, noradrenaline, serotonin, and dopamine metabolism, meant that their use was limited by the hypertensive 'cheese reaction' whereby ingestion of tyramine, as found in cheese, led to marked elevation in tyramine and catecholamines, leading to hypertension. Newer MAO-B selective inhibitors mainly metabolize dopamine and minimize this hypertensive side effect. The phenomenon can still occur with selegiline, due to some MAO-A inhibition at higher doses, but not with rasagiline or safinamide, where there is little MAO-A inhibition. This section will primarily focus on MAO-B selective inhibitors.

Uses

Licensed uses

In the UK/USA

- *PD*.

1. *Rasagiline* is licensed for the treatment of idiopathic PD as monotherapy or as adjunct therapy with or without levodopa in individuals aged 18 years and older.
2. *Safinamide* is licensed for the treatment of idiopathic PD as adjunct therapy to levodopa in patients with motor fluctuations in individuals aged 18 years and older.
3. *Selegiline* is licensed as an adjunct to levodopa therapy in the management of PD, specifically for the treatment of fluctuating motor symptoms, including dyskinesias, and 'end-dose' and 'on–off' phenomena in individuals aged 18 years and older.

Off-label uses

- None.

Mechanism of action

All three agents are selective inhibitors of MAO-B. Rasagiline and selegiline are irreversible inhibitors whilst safinamide is a reversible inhibitor. MAO-B metabolizes dopamine and phenylethylamine. Inhibition results in increased synaptic concentration of dopamine within the PNS and CNS. Safinamide has been shown to also inhibit voltage-gated sodium channels and modulate glutamate release, although it is unclear if these actions have a significant therapeutic impact.

Toxicity and side effects

- *Common—Cardiovascular*: hypotension (including postural). *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, and stomatitis. *Neurological*: confusion, dizziness, dyskinesia, hallucinations, headache, insomnia, somnolence, and vivid dreams.
- *Serious—Cardiovascular*: arrhythmias. *Psychiatric*: psychosis. *Systemic*: serotonin syndrome and tyramine-induced hypertensive crisis.

Contraindications

- *Absolute*: hypersensitivity to MAOIs, severe liver disease, active peptic ulcer disease, concomitant use of other MAOIs, SSRIs (e.g. fluoxetine—5-week washout period advised), meperidine, and pethidine. Drug interactions may lead to risk of serotonin syndrome. Safinamide is contraindicated in individuals with albinism, retinal degeneration, uveitis, inherited retinopathy, or severe progressive diabetic retinopathy, as retinal degeneration was seen in rodents after exposure at therapeutic levels of safinamide. This risk was not identified in further monkey studies or human clinical trials.
- *Relative*: Use with caution in moderative or severe hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustment is routinely required.
- *Pregnancy*: adverse events were observed in some animal reproduction studies and there are no adequate and well-controlled studies in pregnant women. The manufacturers advise avoidance, if possible, in this group.
- *Lactation*: inhibition of prolactin secretion may inhibit lactation. Excretion in breast milk is unknown; hence, as a precaution, the manufacturers advise avoiding use in nursing mothers. Case reports document safe use of 6–10 mg of selegiline during pregnancy with no adverse events, there are no case reports documenting rasagiline or safinamide use.

Efficacy

- *Rasagiline*: there is a good evidence base from several RCTs that rasagiline is effective as both a monotherapy and an adjunct in the management of PD. For example, the *TEMPO* study (TVP-1012 in Early Monotherapy for PD Outpatient trial), an RCT of rasagiline use in levodopa-naïve early PD patients ($n = 404$), lasting 26 weeks, demonstrated that, at 1 mg, there was a reduction of 4.20 units in the UPDRS score, compared to placebo (95% CI −5.66 to −2.73 units; $p < 0.001$), and, at 2 mg, a reduction of 3.56 units (95% CI −5.04 to −2.08 units; $p < 0.001$).

Researchers have suggested that rasagiline may have a neuroprotective effect, based on its antiapoptotic and antioxidant activity. The *ADAGIO* (Attenuation of Disease Progression with Azilect Given Once-daily trial) RCT used a delayed-start design to assess whether rasagiline has disease-modifying properties in early untreated PD. Phase 1 lasted 36 weeks and assigned patients to either rasagiline 1 mg, 2 mg (the early-start groups), or placebo. In phase 2, the early-start groups continued their assigned treatments, and the placebo groups were randomly assigned to either 1 mg or 2 mg rasagiline. The trial suggested there was a beneficial neuroprotective effect of early treatment with rasagiline, compared to delayed treatment, and suggested a disease-modifying effect at the 1 mg dose. However, this was not seen with the 2 mg dose. Due to the conflicting results and the debated validity of the delayed-start trial design in proving neuroprotection, it remains unclear as to whether these results are clinically valid.

- *Safinamide:* the SETTLE study randomized 549 patients with PD and >1.5 h OFF time to 100 mg safinamide or placebo. Mean change in daily on time without troublesome dyskinesia was 1.42 h (baseline of 9.3 h) with safinamide versus 0.57 h (baseline of 9.06 h) with placebo ($p < 0.001$).

- *Selegiline: DATATOP* (Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism)—a multicentre, placebo-controlled trial (*n* = 800) that investigated the effect of selegiline (10 mg/day), tocopherol 2000 iu/day (a compound with vitamin E activity), or placebo in early PD. Selegiline delayed the need for commencement of dopaminergic therapy, and tocopherol did not demonstrate any therapeutic benefit.

A meta-analysis of 17 RCTs (*n* = 3525) concluded that MAO-B inhibitors reduce disability, the need for levodopa (0.57, 0.48–0.67; $p < 0.00001$), and the incidence of motor fluctuations (0.75, 0.59–0.95; $p = 0.02$), without substantial side effects or increased mortality (OR 1.13, 95% CI 0.94–1.34; $p = 0.2$).

The MDS review found selegiline efficacious as a monotherapy. There is insufficient evidence to support a neuroprotective effect of selegiline.

Dosing and monitoring

Dosing

- *Rasagiline*: treatment is with 1 mg od. Dose should be decreased in patients with mild hepatic impairment as well as when taking with ciprofloxacin or other CYP1A2 inhibitors.
- *Safinamide*: start treatment at 50 mg in the morning. This can be increased to 100 mg if required at 2 weeks.
- *Selegiline*: start treatment at 5 mg in the morning. This dose can be increased to a maximum of 10 mg/day, either as a single dose or bd, after 2–4 weeks (1.25 mg of the dissolvable tablet is bioequivalent to 10 mg standard tablet).

Levodopa dose may subsequently be reduced based on symptom control.

Monitoring

- None required.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.34.
Interactions See Table 23.35.

Table 23.34 Pharmacokinetics of MAOIs

	Selegiline	Rasagiline	Safinamide
Main routes of administration	PO	PO	PO
Oral bioavailability	~5%	36%	95%
T_{max}	0.5–2 h	1 h	1.8–2.8 h
Protein binding	90%	88–94%	88–90%
Metabolism	Hepatic, primarily via CYP2B6	Hepatic, primarily via CYP1A2	Hepatic, amidases, not CYP system
Pharmacologically active metabolites	Yes	No	No
Elimination half-life	10 h	1–3 h	20–30 h

Table 23.35 Interactions of MAOIs

Medications which alter MAO-B inhibitor plasma levels	Pharmacodynamic interactions
1. Selegiline Levels increased: contraceptives. 2. Rasagiline: Levels decreased: CYP1A2 inducers, e.g. cyproterone Levels increased: CYP1A2 inhibitors, e.g. ciprofloxacin	With sympathomimetics: may enhance hypertensive effects. With antidepressants and other serotonergic agents: may increase the risk of serotonin syndrome. (see product literature for recommended washout periods) With tramadol: may increase the risk of seizures. With antihypertensives: may increase the risk of orthostatic hypotension

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Mirabegron and vibegron

Mirabegron and vibegron are both selective beta-3-adrenergic receptor agonists licensed for the treatment of OAB. Mirabegron was first licensed for use in 2013 in the UK. Vibegron is a newer agent, available in the USA, but not the UK. They are effective drugs, which have several advantages over anticholinergics, the other group of drugs used for this indication. Unlike anticholinergics, they do not cause dry eyes and dry mouth, and do not have the potential to exacerbate cognitive impairment. There are no large comparator studies that have compared mirabegron and vibegron. Vibegron has less potential interactions with other medications, and has been identified to be the preferred agent for patients in one small crossover study. This is potentially due to a greater reduction in episodes of incontinence seen with vibegron.

Uses

Licensed uses

In the UK/USA

(Licensing is the same for both agents—vibegron is not available in the UK)

- Mirabegron and vibegron are licensed for the symptomatic management of OAB syndrome in individuals aged 18 years and older.

Off-label uses

- None.

Mechanism of action

Mirabegron and vibegron are selective β3-adrenoceptor agonists. They act during the urine storage phase of the urinary bladder fill-void cycle by promoting detrusor muscle relaxation and increasing the volume of urine that can be stored prior to voiding.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension and tachycardia (rarely AF) can be seen with mirabegron, but not vibegron. *Dermatological:* Drug eruption, eczema, and rash. *Gastrointestinal:* Constipation or diarrhoea. *Neurological:* dizziness, headache, and fatigue. *Urology*: urinary retention, UTI.
- *Serious—Dermatological*: Angioedema and leukocytoclastic purpura have rarely been described with mirabegron, but not vibegron.

Contraindications

- *Absolute*: hypersensitivity to the medication or its excipients. Mirabegron is contraindicated in severe uncontrolled hypertension (systolic BP ≥180 mmHg and/or diastolic BP ≥110 mmHg).
- *Relative*: patients with urinary retention or at high risk of urinary retention due to significant bladder outlet obstruction.

Mirabegron: Avoid if eGFR <15 mL/min/1.73 m^2 or if there is concomitant use of strong CYP450 inhibitors and eGFR <30 mL/min/1.73 m^2. Reduce the dose to 25 mg once daily if eGFR 15–30 mL/min/1.73 m^2 or if there is concomitant use of strong CYP450 inhibitors and eGFR 30–89 mL/min/1.73 m^2. Avoid in severe hepatic impairment and in moderate hepatic impairment if there is concomitant use of strong CYP450 inhibitors. Reduce the dose to 25 mg once daily in moderate hepatic impairment, and in mild hepatic impairment if there is concomitant use of strong CYP450 inhibitors.

Vibegron: Avoid in patients with eGFR<15 mL/min/1.73 m^2 and patients with severe hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustments are required in the elderly population.
- *Pregnancy*: preclinical reproductive toxicity studies have reported adverse foetal effects in animals only at levels of systemic exposure significantly higher than would be expected with recommended doses. There have been no controlled studies in humans; the manufacturers

advise avoidance in these populations due to the lack of data. Use only if potential benefits outweigh risks.

- *Lactation*: there is no data on the use of mirabegron or vibegron during breastfeeding in humans. They are highly protein bound and have low oral bioavailability hence large amounts are unlikely to reach the nursing infant. Infants should be monitored for side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

Mirabegron:

Pooled analysis of the first three RCTs to assess the effects of mirabegron on urgency and incontinence in adult patients with OAB showed that, compared to placebo, there was a significant reduction in the number of incontinence and micturition episodes over 24 h. There were 0.4 fewer episodes of incontinence, compared to placebo ($p < 0.001$, mean baseline episodes 2.73, mean change with mirabegron −1.49 vs. −1.1 with placebo); and 0.55 fewer episodes of micturition, compared to placebo ($p < 0.001$, mean baseline episodes 11.58, mean change with mirabegron −1.75 vs. −1.2 with placebo). RCTs have compared mirabegron to tolterodine tartrate MR, with several trials suggesting that mirabegron may be the more effective agent; however, a NICE technology appraisal conducted a Bayesian analysis of mirabegron compared to various anticholinergics and concluded that there was no significant difference between these agents in terms of their effects on urgency and incontinence.

Vibegron:

A phase three randomized, placebo-controlled, double-blind study evaluated the efficacy of vibegron for the treatment of OAB. The study drug met its primary endpoint, the change in micturitions/day at 12 weeks compared to baseline. The change in LS mean micturitions/day was –2.08 and –2.03 for the 50 and 100 mg vibegron doses respectively, and –0.86 for placebo ($p < 0.001$).

Dosing and monitoring

Dosing

Mirabegron: Patients should be started and maintained on the effective dose of 50 mg once daily, with no adjustment routinely required, unless there is renal or hepatic impairment (see Contraindications, earlier).
Vibegron: 75 mg once daily is the standard dose.

Monitoring

BP should be measured at baseline and then regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.36.
Interactions See Table 23.37.

Table 23.36 Pharmacokinetics of mirabegron and vibegron

	Mirabegron	Vibegron
Bioavailability	29–35%	Not known
T_{max}	3–4 h	1–3 h
Protein binding	71%	50%
Metabolism	Hepatic	Hepatic, mainly CYP3A4
Pharmacologically active metabolites	No	No
Elimination half-life	~50 h	~30.8 h
Excretion	Urine, mainly as unchanged drug (55%), faeces (34%)	Faeces (59%) and urine (20%)

Table 23.37 Interactions of mirabegron and vibegron

Medications which alter plasma levels of mirabegron and vibegron	Medications whose plasma levels are altered by mirabegron and vibegron	Pharmacodynamic interactions
Mirabegron only: **Levels increased:** CYP3A inhibitors, e.g. clarithromycin and ketoconazole. **Levels decreased:** CYP3A inducers, e.g. rifampicin, may reduce plasma levels	**Mirabegron and vibegron:** **Levels increased:** digoxin	**Mirabegron and vibegron:** **With anticholinergics:** increased risk of urinary retention **Mirabegron only:** **With drugs which prolong the QT interval:** increased risk of ventricular arrhythmia

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Non-steroidal anti-inflammatory drugs

Aspirin, or acetylsalicylic acid, was the first NSAID to be synthesized in the mid-nineteenth century. There are >20 NSAIDs available today. Those licensed for use in migraine include diclofenac, ibuprofen, and tolfenamic acid. Indometacin/indomethacin is also commonly used in headache disorders. It has a prominent role in specific headache disorders, including trigeminal autonomic cephalalgia (TACs).

Aspirin is also employed extensively for its antiplatelet effects. Its use is detailed separately in its own monograph; see p. 516.

Uses

Licensed uses

In the UK/USA

- Migraine.

1. *Diclofenac*: is licensed for the treatment of migraine in individuals aged 18 years and older.
2. *Ibuprofen*: is licensed for the management of acute migraine in individuals aged 12 years and older.

In the USA

- Migraine.

1. *Diclofenac*: is licensed for the treatment of migraine in individuals aged 18 years and older.

- Analgesia.

1. *Ibuprofen*: is licensed for the management of mild-to-moderate pain in individuals aged 6 months and older.

In the UK/USA

1. *Indometacin* has no licensed neurological use.

Off-label uses

1. *Diclofenac*: other headache disorders.
2. *Ibuprofen*: none.
3. *Indometacin*: can be used in the acute management of indometacin-responsive headaches, including Hemicrania continua (HC), Paroxysmal hemicrania (PH), primary stabbing headache, and Valsalva-induced headache.

Mechanism of action

NSAIDs inhibit the cyclo-oxygenase (COX) enzymes COX-1 and COX-2. The COX enzymes convert arachidonic acid to prostaglandins and thromboxanes, both of which are the end-products of fatty acid metabolism and are involved in a number of biologically important processes, including gastric protection, inflammation, pain, fever, platelet aggregation, and vascular homeostasis. Inhibition of COX-2 is believed to be responsible for the anti-inflammatory, analgesic, and antipyretic properties of NSAIDs. COX-1 is found in almost all tissues and has a number of roles, including gastric protection. Inhibition of this enzyme is thought to result in the majority of use-limiting side effects of NSAIDs, including gastric ulceration. NSAIDs differ with respect to their differential activity at COX enzymes and their pharmacokinetics.

Toxicity and side effects

- *Common—Dermatological*: maculopapular rash, urticaria. *Gastrointestinal*: diarrhoea, dyspepsia, nausea, vomiting. *Neurological*: dizziness, drowsiness, headache, tinnitus, vertigo.
- *Serious—Cardiovascular*: MI, fluid retention resulting in new or worsening heart failure. *Dermatological*: Stevens–Johnson syndrome, toxic epidermal necrolysis. *Gastrointestinal*: peptic ulcer disease. *Haematological*: aplastic anaemia. *Neurological*: aseptic meningitis is sometimes seen, usually in patients with connective tissue disorders such as SLE. Cognitive impairment, convulsions, and stroke. *Renal*: interstitial nephritis, papillary necrosis, renal cell cancer. *Respiratory*: anaphylaxis, bronchospasm. *Psychiatric*: psychosis.

Contraindications

- *Absolute*: active gastrointestinal bleeding/ulceration, asthma if known to experience bronchospasm with NSAIDs, coagulopathy, hypersensitivity to aspirin or any other NSAID.
- *Relative*: inflammatory bowel disease can be worsened by NSAIDs. NSAIDs should be avoided in patients with pre-existing heart failure, ischaemic heart disease, and liver and renal failure.

Uses in special populations

- *Elderly*: NSAIDs should be used with caution in the elderly, as they are more likely to have renal impairment and cardiovascular disease. Polypharmacy is also more common in the elderly population, and NSAIDs have multiple drug interactions. NSAIDs should only be used if absolutely necessary and in the smallest effective dose for the shortest time possible.
- *Pregnancy*: NSAIDs should be avoided in the last trimester, due to a risk of early closure of the ductus arteriosus, oligohydramnios, renal dysfunction, and, particularly in premature infants, intracranial haemorrhage. With regard to the rest of pregnancy, NSAIDs should be avoided, unless the benefits outweigh the risks.
- *Lactation*: NSAIDs are present in small amounts in breast milk but are not believed to pose a risk to the neonate. It should, however, be used with caution in lactating mothers.

Efficacy

1. *Diclofenac—migraine*: a Cochrane review looking at diclofenac potassium 50 mg vs. placebo in the acute management of migraine found that the NNT for patients to be pain-free at 2 h was 6.2, and to be pain-free at 24 h 9.5. There was no difference between diclofenac 50 mg and placebo for adverse events. In about half of those treated (55%), there was a significant reduction in pain at 2 h from moderate/severe to mild, while 22% of patients had no pain at 2 h. The review concluded that diclofenac potassium 50 mg was a suitable oral

treatment for acute migraine attacks. A network meta-analysis of 88 studies determined that diclofenac was the most effective treatment with regards to 2 h pain relief but was also the most likely to require subsequent rescue medication. This study concluded that diclofenac was the best NSAID for migraine treatment when all endpoints were considered for comprehensive treatment.

2. *Ibuprofen—migraine*: a Cochrane review of ibuprofen in the management of acute migraine found that a single 400 mg dose of ibuprofen significantly reduced headache from moderate/severe to no headache at 2 h in 26% of patients, compared with 12% for placebo. The NNT was 7.2. Twenty per cent of patients were headache-free at 2 h with ibuprofen 200 mg (NNT 9.7). The 400 mg dose was more effective than 200 mg at reducing headache severity ($p = 0.0002$). Adverse effects were minimal, and there was no significant difference between placebo and ibuprofen. In a meta-analysis of ibuprofen in acute migraine, the 400 mg dose was found to significantly reduce photophobia by 30% ($p <0.01$) and phonophobia by 49% ($p <0.0001$), compared with placebo. A network meta-analysis of 88 studies determined that ibuprofen exhibited the most desirable tolerability profile among the 10 medications studied.
3. *Indometacin*: there are no RCTs assessing the use of indometacin in headache syndromes. *PH*: a retrospective case note study looking at indometacin use in 74 patients with chronic PH found that 30 patients had a reliable response to indometacin therapy, while the rest either had inconsistent responses or data were unavailable. Of the 30 who responded to indometacin, 24 responded completely.

Dosing and monitoring

Dosing

1. *Diclofenac*: 50 mg of diclofenac should be given at the onset of headache, and, if needed, a repeat dose can be given 2 h later.
2. *Ibuprofen*: a single dose of 200 mg or 400 mg should be taken as soon as possible after the start of migraine.
3. *Indometacin*: start treatment at 75 mg daily in divided doses, usually 25 mg TDS. If there is no response or only a partial response after 48–72 h, then the dose can be increased to a total of 150 mg daily, and then to a further 225 mg/day if there is no response after another 48–72 h period. The drug is typically trialled for ~2 weeks at the highest tolerated dose before the absence of a beneficial response is considered a treatment failure. A response is usually seen within 48–72 h of initiation.

Monitoring

1. *Diclofenac/Ibuprofen*: routine monitoring is not required for diclofenac in the acute management of migraine.
2. *Indometacin*: the regular use of indometacin is associated with severe toxicity, with 10% of patients experiencing a serious adverse effect. Patients should be monitored for hepatic, renal, gastrointestinal, and haematological toxic effects. In particular, patients are at risk of aplastic anaemia and agranulocytosis, and should be monitored for this with regular FBCs.

Pharmacokinetics and interactions

Pharmacokinetics

NSAIDs are absorbed fully and have little first-pass metabolism and small volumes of distribution. Most are highly bound to albumin. They differ in their half-lives: diclofenac (~1 h), ibuprofen (~2 h), and indometacin (~4.5 h). NSAIDs are eliminated by the kidney, after glucuronidation and/or transformation by the liver cytochrome P450 system. Very little of the drug is excreted unchanged (<5%).

Interactions

See Table 23.38.

Table 23.38 Interactions of NSAIDs

Medications which alter NSAID plasma levels	Medications whose plasma levels are altered by NSAIDs	Pharmacodynamic interactions
Levels increased: diclofenac: ciclosporin and imatinib; ibuprofen: azole antifungals; indometacin: diflunisal and probenecid	**Levels increased:** baclofen, digoxin, warfarin, lithium, and methotrexate	**With ACE inhibitors/ angiotensin receptor blockers, calcineurin inhibitors, and diuretics:** renal toxicity **With antidepressants (SSRIs and venlafaxine), anticoagulants, antiplatelets, and corticosteroids:** increased risk of bleeding **With antihypertensives:** NSAIDs antagonize hypotensive effect. **With potassium-sparing diuretics:** increased risk of hyperkalaemia **With quinolones:** increased risk of seizures **With sulfonylureas:** concomitant use can induce hypoglycaemia

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Opioids

Opioids are among some of the world's oldest known drugs. The medical and recreational use of opium dates to at least 4000 BC. Morphine and other opioid drugs, both naturally occurring opiates and synthetic opioids, act by binding to the opiate receptors μ, κ, and δ. Morphine predominantly produces its analgesic and euphoric effects through the μ-opioid receptor.
In neuropathic pain, the most studied opioid drugs are fentanyl, morphine, oxycodone, and tramadol. Although opioid drugs generally provide very good analgesia, their long-term use is restricted by their side effect profile and the risks of substance misuse and tolerance.

Uses

Licensed uses

- Pain.

In the UK/USA

1. *Fentanyl.*

Fentanyl is licensed for malignant and non-malignant chronic intractable pain in individuals above the age of 2 years. IV preparations are only licensed for use in individuals above the age of 12 years. Buccal preparations are licensed for chronic cancer pain in opioid-tolerant patients above the age of 16.

2. *Morphine.*

In the UK, PO morphine is licensed for the treatment of moderate-to-severe pain in individuals above the age of 1 year. Note that Oramorph® solution and MXL® capsules are not licensed for use in children under 1 year; Filnarine® SR and Sevredol® tablets are not licensed for use in children under 3 years, and MST Continus® preparations are only licensed in children to treat cancer pain. In the USA, oral morphine is licensed for the treatment of moderate-to-severe pain in adults.

3. *Oxycodone*.

Oxycodone is licensed for moderate-to-severe pain in individuals above 18 years of age.

4. *Tramadol*.

Tramadol is licensed for moderate-to-severe pain in individuals over the age of 12 years (UK)/16 years (USA).

Off-label uses

- RLS.

Mechanism of action

Morphine and oxycodone are the most studied opioids in the context of neuropathic pain. Both are μ-opioid receptor agonists. Oxycodone also antagonizes κ-opioid receptors. Fentanyl is a very potent μ-opioid receptor agonist. The overall effect of opioid drugs is to reduce nociceptive transmission.

Toxicity and side effects

- *Common—Cardiovascular*: bradycardia, oedema, palpitations, postural hypotension, tachycardia. *Dermatological*: flushing, pruritus, rash, sweating, urticaria. *Gastrointestinal*: biliary spasm, constipation, dry mouth, nausea, vomiting. *Neurological*: confusion, dizziness, drowsiness, headache, vertigo. *Ophthalmological*: miosis, visual disturbance. *Psychiatric*: dependence, dysphoria, euphoria, hallucinations, mood changes, sleep disturbances. *Respiratory*: bronchospasm. *Urological*: difficulty with micturition, ureteric spasm, urinary retention.

Note: With larger doses, muscle rigidity and hypotension occur. Tolerance and substance abuse preclude long-term usage.

- *Serious—Gastrointestinal*: paralytic ileus. *Neurological*: seizures. *Respiratory*: respiratory depression.

Contraindications

- *Absolute*: any patients with acute respiratory depression, paralytic ileus, raised ICP, and head injuries (impairs assessment of pupillary responses); comatose patients.
- *Relative*: reduce dose in hepatic impairment (risk of precipitating encephalopathy); reduce dose in renal impairment (increased and prolonged effect, and increased cerebral sensitivity), impaired consciousness, COPD, acute asthma, hypotension, shock, MG, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders. Reduce dose in the elderly, hypothyroidism, and adrenocortical insufficiency. Caution is recommended if prescribing opiates to patients with a history of drug dependence. Tramadol can lower the seizure threshold and should be avoided in epilepsy.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and benefit from halving the adult dosing regimen.
- *Pregnancy*: opiates depress neonatal respiration; Neonates of dependent mothers may demonstrate withdrawal effects. Opiates may increase rates of specific malformations but the evidence is unclear and frequently conflicting. An association with reduced foetal growth and strabismus has also been reported. Use if benefits outweigh risks in pregnancy.
- *Lactation*: therapeutic doses of morphine, tramadol, and fentanyl are unlikely to affect the breastfeeding infant; however, there is a small potential of withdrawal symptoms in infants of dependent mothers. Use if benefits outweigh risks. Oxycodone is present in breast milk. Infant sedation occurs commonly with maternal use, and there is a risk of infant CNS depression and death. Neonates have a reduced clearance of oxycodone. Only use if benefits outweigh the risk, and there is no alternative analgesic. A maximum maternal dose of 30 mg/day is recommended, and the infant should be monitored for drowsiness, adequate weight gain, and developmental milestones.

Efficacy

Fentanyl: A Cochrane systematic review only found 1 clinical trial assessing the efficacy of fentanyl (as single dermal patches) for the treatment of neuropathic pain in adults compared to placebo. They concluded that due to the unusual design of the study and low participant number (n = 163) there is no good evidence to support or refute the use of fentanyl in neuropathic pain.

Morphine: A Cochrane review of morphine for chronic neuropathic pain found that the low quality of the studies available did not provide a reliable indication of the effect. Additionally, the small size of studies may overestimate the treatment effect. A further systematic review demonstrated that both IV and PO morphine were effective in the treatment of phantom limb pain both in the short and long term. Opioid drugs are viewed as non-superior to TCAs by both the EFNS and NICE. It is recommended that they are used second or third line and only for a short duration when antidepressants and anticonvulsants have failed.

Oxycodone: A Cochrane review identified 5 placebo-controlled studies (2 cross-over designs and 3 parallel-group designs) (n = 637 with painful diabetic neuropathy and n = 50 with post-herpetic neuralgia). A 'moderate benefit' (at least 30% pain relief) was reported in 44% of subjects in 3 trials of painful diabetic neuropathy (n = 537) treated with oxycodone compared with 27% with placebo. NNT of 5.7. The review concluded that there was very low-quality evidence to support that oxycodone had efficacy in the treatment of painful diabetic neuropathy or post-herpetic neuralgia.

Tramadol: A Cochrane systematic review identified 6 RCTs (n = 438 with moderate-to-severe neuropathic pain) that randomized patients to 100 mg tramadol daily increased to 400 mg daily (or maximum tolerated dose) over 1–2 weeks against placebo. 53% of subjects reported at least a 50% pain reduction in 3 studies, compared to 30% of patients with placebo. The risk ratio was 2.2 (95% CI 1.02–4.6). The NNT was 4.4 (95% CI 2.9–8.8). A further meta-analysis (303 total participants) showed that tramadol was more effective than placebo in achieving >50% pain relief, with an NNT of 3.8 (95% CI 2.8–6.3). Tramadol is recommended by the EFNS as a second- or third-line analgesic for the long-term treatment of neuropathic pain, but it can be used as a first-line option for acute exacerbations of painful diabetic neuropathy.

Dosing and monitoring

Consideration of the following factors must be taken into account when starting a patient on an opioid drug: total daily dose, potency, patient's degree of opioid tolerance, patient co-morbidities, concurrent medications, and type and severity of pain.

For converting dosages between opioids, see Table 23.39.

Dosing

1. *Fentanyl*—for fentanyl transdermal patches: start treatment at 12–25 micrograms/h patch every 72 h. Base dose increments on the daily dose of supplementary opioid analgesics. Maximal analgesia will be achieved after 24 h, so consider using a short-acting opioid as breakthrough analgesia until this time.

Table 23.39 Opioid drug dose conversions

Fentanyl: transdermal	Morphine: oral	Oxycodone: oral	Tramadol: oral
12.5 micrograms/h	30–59 mg/24 h	15–29.5 mg/24 h	150–300 mg/24 h
25 micrograms/h	60–134 mg/24 h	30–67 mg/24 h	301–600 mg/24 h
50 micrograms/h	135–224 mg/24 h	67.5–112 mg/24 h	NA
75 micrograms/h	225–314 mg/24 h	112.5–157 mg/24 h	NA
100 micrograms/h	315–404 mg/24 h	157.5–202 mg/24 h	NA

NA, information not available.

2. *Morphine*—starting dose: po 5–10 mg every 4 h, as required. The parenteral dose is approximately three times as strong as the oral dose. Initially, titrate with short-acting formulations; when an average daily dose is established, convert to longer-acting opioids or transdermal applications. To convert to extended-release preparations, administer 50% of the patient's 24 h requirement bd or one-third of the daily morphine dosage tds.
3. *Oxycodone*—starting dose: for immediate-release preparations, 2.5–5 mg po every 4–6 h. Trial 4–6 weeks. Increase the dose slowly, as required. Doses >30 mg daily are rarely needed. Maximum dose 400 mg/24 h, but some patients will require higher doses. Patients on high long-term doses of oxycodone should be converted to a sustained-release preparation. Halve the oral dose if administering parenterally.
4. *Tramadol*—for the treatment of neuropathic pain, start treatment at 25 mg every morning. Up titrate by 25 mg every 3 days, in separate doses, to reach a qds regimen (25 mg qds). Then increase the total daily dose by 50 mg every 3 days. Trial for 4 weeks. Note, if a more rapid onset of analgesic effect is required, patients can be started on 50–100 mg tramadol every 4–6 h. Maximum dose 400 mg daily. In patients with chronic pain, sustained-release preparations can be used, with an initial dose of 100 mg daily, increased every 5 days by 100 mg to a maximum dose of 300 mg daily.

Monitoring

None required.

Pharmacokinetics and interactions

Pharmacokinetics

See Table 23.40.

Interactions

See Table 23.41.

Table 23.40 Pharmacokinetics of opioids

	Fentanyl	Morphine	Oxycodone	Tramadol
Main routes of administration	BC/IN/IV/SC/SL/TD	IV/IM/SC/PO	IV/IM/SC/PO	PO (IV/IM)
Oral bioavailability	50–90% for BC/SL/TD routes	20–40%	95–100%	75–95%
T_{max}	BC: 35–45 minSL: 45 min to 1.5 h TD: 20–72 h	SC/IM: 20 minPO: 30–90 min	PO: 1 hFor modified release preparations: PO, 3 h	PO: 10–12 h
Protein binding	80–85%	30–35%	45%	20%
Time to steady state	IV: 18–24 hTD: 144 h	24 h	18–24 h	4 days
Pharmacologically active metabolites	No	Yes, strong activity	Yes, strong activity	Yes, strong activity
Elimination half-life	IV: 219 minBC: 2–11 h SL: 7–15 h TD: 13–22 h	2–4 h	3–4 h	6–10 h
Metabolism	CYP3A4	UDP-glucuronosyltransferase-2B7	CYP2D6, CYP3A4	CYP2B6, CYP2D6, CYP3A4
Excretion	As metabolites: urine >90%, faecal 1% Unchanged: urine 7%	As metabolites: urine 80%, faeces 10% Unchanged: urine 10%	As metabolites: urine 65% Unchanged: urine 20%	As metabolites: urine 60% Unchanged: urine 30%

BC, buccal; IN, intranasal; IV, intravenous; PO, oral; PR, per rectum; SC, subcutaneous; SL, sublingual; TD, transdermal.

Table 23.41 Interactions of opioids

Medications which alter opioid drug plasma levels	Medications whose plasma levels are altered by opioid drugs	Pharmacodynamic interactions
Levels decreased: CYP450 enzyme inducers, e.g. carbamazepine, phenytoin. **Levels increased:** fentanyl: CYP450 enzyme inhibitors, e.g. cimetidine, macrolide antibiotics, ritonavir, and triazoles; oxycodone: voriconazole	**Levels decreased:** none. **Levels increased:** fentanyl: etomidate; morphine: esmolol and gabapentin	**With alcohol, antihistamines, antipsychotics, baclofen, and benzodiazepines:** enhanced sedative and often hypotensive effects **With coumarins:** tramadol enhances the anticoagulant effect. **With MAOIs, SNRIs, and SSRIs:** tramadol enhances serotonergic effects. **With domperidone and metoclopramide:** antagonism of gastric emptying.

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Orexin receptor antagonists

The orexin receptor antagonists are a new group of medications approved for the treatment of sleep onset and sleep maintenance insomnia. They are effective drugs, which have a number of potential advantages over older classes of drugs such as benzodiazepines and Z-drugs, which have the same indication but act on GABA receptors. They appear to have very little predisposition to dependence or tolerance, and do not cause respiratory depression. Suvorexant was the first agent to be approved in the USA in 2014. They are not currently available in the UK.

Uses

Licensed uses

In the USA (Not available in the UK)
Daridorexant, lemborexant, and suvorexant are approved for the same indication: the treatment of sleep onset or sleep maintenance insomnia in individuals aged 18 years and older.

Off-label uses
Insomnia in respiratory disorders such as obstructive sleep apnoea (OSA), and irregular sleep-wake rhythm disorder

Mechanism of action

The orexin receptor antagonists act by blocking the action of orexin A and B on both orexin 1 and 2 receptors. The orexin neuropeptides are important for maintaining wakefulness, hence antagonism of this pathway supresses the wake drive and improves insomnia.

Toxicity and side effects

- *Common—Gastrointestinal:* diarrhoea and dry mouth. *Neurological*: abnormal dreams, dizziness, headache, hypnogogic/hypnopompic hallucinations, non-rapid eye movement (NREM) parasomnias, sleep paralysis, and somnolence. *Respiratory:* Upper respiratory tract infections.
- *Serious—Psychiatric*: Increase in suicidal ideation (rare).

Contraindications

- *Absolute*: known hypersensitivity to the drug or its constituents, and narcolepsy.
- *Relative*: Co-administration with other CNS depressants. Orexin antagonists can affect driving ability the next day, hence patients should not drive if they still feel sleepy. Patients with pre-existing NREM parasomnias and suicidal ideation could worsen with treatment. Reduced doses should be used in moderate hepatic impairment and these medications should not be used in severe hepatic impairment. No dose adjustments are required in renal impairment.

Use in special populations

- *Elderly*: no specific dose alterations are required. Caution should be taken, as the elderly experience an age-related decline in renal and hepatic function and may be more prone to falls and somnolence.
- *Pregnancy*: limited data are available for the safety of these agents in pregnancy. Animal models suggested that the orexin antagonists induce toxicity only at very high multiples of the maximum recommended human dose. Given the lack of data use only if the potential benefits outweigh the risks.
- *Lactation*: There are no data from human studies. All of the medications are present in rodent milk, and are predicted to be present in human milk. Use if potential benefits outweigh risks and monitor the infant for somnolence.

Efficacy

Daridorexant: Two multicentre, randomized, double-blind, placebo-controlled trials investigated the use of daridorexant for the treatment of insomnia. The primary endpoints: baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS) were significantly improved at both 25 and 50 mg doses of daridorexant compared to placebo (50 mg –22.8 mins for WASO, and –11.4 mins for LPS ($p < 0.0001$ for both outcomes).

Lemborexant: A randomized, double-blind, placebo-controlled study investigated the use of lemborexant in the treatment of insomnia. The decrease in median LPS with lemborexant ranged from 7 to 17.3 min, with a dose-dependent increase in effect between 1 and 25 mg, when compared to placebo ($p < 0.001$ for doses ≥10 mg). WASO improved by 2.3 to 29.3 mins, with a dose-dependent increase in effects between 2.5 and 15 mg when compared to placebo ($p < 0.1$ for doses ≥15 mg).

Suvorexant: Two multicentre, randomized, double-blind, placebo-controlled trials investigated the use of suvorexant in the treatment of insomnia. Pooled data from both 15 mg and 20 mg groups compared with placebo, demonstrated that treatment with suvorexant resulted led to an improvement in LPS of –11.2 min ($p < 0.001$) and WASO of –5.3 min ($p < 0.01$), when compared with placebo.

Dosing and monitoring

Dosing

The lowest dose should be trialled first, and the dose titrated up to clinical effect. Patients should be advised to ensure that there are at least 7 h until planned awakening before taking the dose.

Daridorexant: Take 25 or 50 mg 30 min before going to bed.
Lemborexant: Take 5 or 10 mg immediately before going to bed.
Suvorexant: Take 5 or 10 mg immediately before going to bed. If the dose is not effective, it can be increased to 15 or 20 mg.

Monitoring

No specific monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.42.
Interactions See Table 23.43.

Table 23.42 Pharmacokinetics of orexin receptor antagonists

	Daridorexant	Lemborexant	Suvorexant
Bioavailability	62%	80–100%	82%
T_{max}	1–2 h	1–3 h	2 h
Protein binding	99.7%	94%	>99%
Metabolism	Hepatic, mainly CYP3A4	Hepatic, mainly CYP3A4	Hepatic, mainly CYP3A
Pharmacologically active metabolites	No	No	No
Elimination half-life	8 h	17–19 h	12 h
Excretion	Faeces 57%, urine 28%	Faeces 57%, urine 29%	Faeces 66%, urine 23%

Table 23.43 Interactions of orexin receptor antagonists

Medications which alter plasma levels of orexin receptor antagonists	Medications whose plasma levels may be altered by orexin receptor antagonists	Pharmacodynamic interactions
Levels decreased: CYP3A inducers, e.g. carbamazepine, phenytoin, and St John's wort **Levels increased**: CYP3A inhibitors, e.g. ketoconazole and ciprofloxacin	**Levels increased:** *Lemborexant:* CYP2B6 substrates e.g. bupropion, methadone *Suvorexant:* Digoxin	**With other CNS depressants, including alcohol**: increased psychomotor impairment and sedative effect

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S1P receptor modulators; including fingolimod, ozanimod, ponesimod, and siponimod

Sphingosine 1-phosphate receptor modulators (S1PR) are a group of oral disease-modifying drugs used in the treatment of MS. Fingolimod was first introduced in 2010, and compared to newer agents has a broader activity against different S1P receptor subtypes. Siponimod is the only agent of this class licensed specifically for secondary progressive MS, although individuals need to have evidence of active disease on neuroimaging (see indications). All of the drugs in this class have the potential to cause bradyarrhythmia after the first dose. This requires monitoring for at least 6 h in the case of fingolimod, whilst the other agents are administered by using a slow up-titration protocol, which minimizes this effect and mitigates against the need for first-dose monitoring for most patients.

Uses

Licensed uses

In the UK

- Fingolimod
- *Highly active RRMS*: fingolimod is licensed for ‘rapidly evolving severe’ RRMS and for RRMS with ‘high disease activity despite treatment’.
  - *Rapidly evolving severe* RRMS is defined as two or more disabling relapses in 1 year, with at least one gadolinium-enhancing lesion on brain MRI or a significant increase in T2 lesion load.
  - *High disease activity despite treatment* is defined as either having at least one relapse in the previous year on IFN-β or glatiramer acetate and at least nine T2-hyperintense lesions in brain MRI or one gadolinium-enhancing lesion. This includes patients with unchanged/increased relapse rate or ongoing severe relapses, as compared to the previous year.

However, NICE guidelines only support the prescription of fingolimod for the second category, i.e. highly active RRMS despite IFN-β or glatiramer therapy.

Ozanimod/ ponesimod

- Ozanimod is licensed for the treatment of RRMS with active disease as defined by the presence of clinical or imaging features, in individuals aged 18 years and over.

Siponimod

- Siponimod is licensed for the treatment of patients with secondary progressive MS with active disease based on clinical or imaging features in individuals over the age of 18.

In the USA

Fingolimod/ ozanimod/ ponesimod/siponimod

- The S1PR modulators are licensed for the treatment of relapsing MS, including clinically isolated syndrome, RRMS and active secondary progressive disease in individuals aged 18 years and older (with the exception of fingolimod, which is licensed for use in individuals aged 18 years and older).
- ***Off-label uses***
- None

Mechanism of action

The S1P receptor modulators induce internalization of the S1P receptor on the surface of lymphocytes and neurons. This disrupts the mechanism by which naïve T cells are drawn from a low concentration of S1P in lymph nodes to a higher concentration of S1P in the circulation. These drugs therefore prevent lymphocyte (i.e. pro-inflammatory Th17 cells) migration to the CNS by sequestration in secondary lymphoid tissues. They lead to a redistribution, instead of a depletion, of lymphocytes. They may also cross the blood–brain barrier and act on S1P receptors expressed by different types of cells within the CNS. Effector memory T cells are not sequestered and may have increased immunosuppressive functions. Fingolimod is active at S1PR1, 3, 4, and 5, whilst ponesimod is specific for S1PR1, and ozanimod and ponesimod only have activity at S1PR1 and 5 receptors. The second-generation S1PR modulators, i.e. all medications other than fingolimod, were designed to minimize activity at the S1PR3 receptor, which was thought to minimize bradycardia and heart block seen with fingolimod. However, some of this effect is also seen with activity at S1PR1 receptors, hence even the second-generation medications require slow up-titration to reduce the risk of bradycardia.

Toxicity and side effects

- *Common—cardiovascular*: bradycardia and hypertension. *Dermatological*: alopecia, eczema, herpes simplex infection, and pruritus. *Endocrine*: hypertriglyceridemia and weight loss. *Gastrointestinal*: Abdominal pain, diarrhoea, and elevated LFTs. *Haematological*: Leucopenia. *Musculoskeletal*: Back pain. *Neurological*: Asthenia, dizziness, drowsiness, headache, migraine, and paraesthesiae. *Ophthalmological*: Blurred vision and eye pain. *Psychiatric*: Depression. *Respiratory*: Bronchitis, cough, dyspnoea, influenza, and sinusitis.
- *Serious—cardiovascular*: AV block. *Haematological*: Increased risk of B and T cell lymphoma. *Immunological*: Increased risk of all infections, particularly herpes infections, and there is an increased risk of progressive multifocal leukoencephalopathy. *Neurological*: posterior reversible encephalopathy syndrome (PRES), seizures, and tumefactive demyelinating lesions. *Ophthalmological*: Macular oedema (increased risk with diabetes mellitus and uveitis).

Contraindications

- *Absolute*: Pre-existing immunodeficiency, hypersensitivity, severe active infection, active chronic infections, severe hepatic impairment (Child–Pugh class C), patients who have had a transient ischaemic attack (TIA) or stroke in the last 6 months and patients with active malignancy (excluding basal cell carcinoma). Cardiac contraindications include individuals who, in the previous 6 months have had an MI, unstable angina, decompensated heart failure or New York Heart Failure Association class III/IV. Patients with a QTc of >500 ms, sick sinus syndrome, or heart block; second-degree Mobitz type or third-degree heart block, and any cardiac arrythmias requiring antiarrhythmic treatment with class Ia or III antiarrhythmics.
- *Siponimod*: Patients homozygous for CYP2C9*3*3 (poor metabolizer).
- *Relative*: Patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope, or previous cardiac arrest, QTc interval >460 msec (female), >450 ms (male), uncontrolled bradycardia, uncontrolled hypertension, or severe sleep apnoea. Severe respiratory disease. Caution should be used during initiation in patients with mild or moderate hepatic impairment, but no dose adjustments are required. This drug has not been studied in patients with renal impairment, but no dose adjustments are necessary.

Use in special populations

- *Elderly*: The S1P receptor modulators have not been specifically studied in the elderly. They should be used with caution in the elderly, as co-morbidities such as cardiovascular disease, diabetes, and hypertension are more common, meaning the elderly are likely to experience more side effects than younger adults.
- *Pregnancy*: Fingolimod is teratogenic, with increased rates of cardiac, renal, and musculoskeletal abnormalities in offspring. There is limited data on the use of other S1P receptor modulators in pregnancy, although animal models suggest there may be similar adverse effects to fingolimod. These agents should not be used during pregnancy. A negative pregnancy test is required prior to initiation, and active contraception should be used during, and for a short period following treatment, depending on the elimination time of the drug. Following discontinuation patients should not get pregnant for 2 months for fingolimod, 3 months for ozanimod, 1 week for ponesimod, and 10 days for siponimod.
- *Lactation*: The risk of S1P receptor modulators entering breastmilk is relatively low as they are all highly protein-bound in maternal plasma. However, even though the overall amount absorbed by the infant is likely to be low, due to the potential risks, breastfeeding is not recommended.

Efficacy

Fingolimod: Multiple studies to date on adult RRMS patients have provided data substantiating fingolimod efficacy, with significant impacts on clinical and radiological outcomes. The *FREEDOMS* trial demonstrated a 54% reduction in ARR, compared with placebo, a significant reduction in risk of disability progression sustained at 3 and 6 months, and 30% reduction in rate of brain volume loss on MRI that persisted for 4 years (*FREEDOMS* extension phase). The *FREEDOMS II* trial further validated the safety and efficacy of fingolimod in decreasing relapse rates, with a 48% reduction compared with placebo. The *TRANSFORMS* trial showed a relative reduction in ARR of 38–52% with fingolimod, compared to IFN-β 1a, and fewer new and enlarging MRI lesions and less brain atrophy. A recent review of 6 RCTs found that fingolimod effectively decreased inflammatory disease activity but had less clear effects on disability worsening.

Ozanimod: Two large randomized controlled trials compared ozanimod with interferon beta1a over 1 and 2 years (SUNBEAM and RADIANCE respectively). The relative reduction in the annualized relapse rate was 48% at 1 year and 38% at 2 years ($p < 0.0001$). The studies also demonstrated a significant reduction in T2 hyperintense and T1 gadolinium-enhancing lesions compared to interferon.

Ponesimod: OPTIMUM, a large randomized controlled trial compared the efficacy of ponesimod with teriflunomide 14 mg over 108 weeks. The relative reduction in the annualized relapse rate was 30.5% ($p = 0.0003$). The study also demonstrated a significant reduction in the number of active radiological lesions.

Siponimod: EXPAND was a double-blind, placebo-controlled trial that evaluated the ability of siponimod at 2 mg to slow the progression of patients with secondary progressive MS. To enter the trial the patient cohort had to be aged <61 years, and have evidence of progression over 2 years (in the absence or in spite of clinical relapses), and had to have active features on MRI head, i.e. gadolinium-enhancing lesions or new T2 lesions. Follow-up was for 37 months. The primary outcome was confirmed disability progression (CDP), as defined by at least a 1-point increase in baseline expanded disability status scale (EDSS) if EDSS at baseline 5 or less, or 0.5-point increase if EDSS at baseline 5.5 or more, sustained for 3 months. After 37 months the relative risk reduction in patients with 3-month CDP was 21% ($P=0.0134$) i.e. 26.3% vs. 31.7% with placebo. There was also a significant reduction in active lesions present on serial MRIs, and a slower rate of brain atrophy when compared to placebo.

Dosing and monitoring

Dosing

Fingolimod: The drug is available as an oral capsule of 0.5 mg od to adults and paediatric patients (≥ 10 years old) weighing >40 kg.

Ozanimod: The drug is available as an oral capsule. Patients take 0.23 mg od for 4 days, 0.46 mg od for 3 days and 0.92 mg od thereafter.

Ponesimod: The drug is available as an oral tablet. Patients take 2 mg for 2 days, then 3 mg for 2 days, then 4 mg for 2 days, then increase by 1 mg every day until they reach a dose of 10 mg. After taking 10 mg for 3 days, the dose is then increased to the usual maintenance dose of 20 mg od.

Siponimod: The drug is available as an oral tablet. Patients take 0.25 mg on day one and then increase, by 0.25 mg a day until they reach a dose of 1.25 mg od. On day 6 they then take the usual maintenance dose of 2 mg od (with the caveat that some patients need a lower maintenance dose depending on their CYP2C9 status—see monitoring).

Monitoring

First-dose monitoring:

1. *Fingolimod:* All patients should be observed for first-dose bradycardia for at least 6 h following their first dose (or if the dose is increased from 0.25 to 0.5 mg). After this, there is de-sensitization of cardiac S1P receptors and the bradycardia resolves. If the heart rate is at its lowest point at 6 h, monitoring should be continued until it begins to improve. If a heart block develops, monitoring should continue until this resolves.

2. *Ozanimod/Ponesimod/Siponimod*: First-dose monitoring should be undertaken as per fingolimod if patients have pre-existing cardiovascular conditions. If these are absent then the slow up-titration protocol makes this risk very unlikely and hence cardiac monitoring is not required.

Long-term monitoring:

Lymphocyte counts:

A dose-dependent reduction of the peripheral lymphocyte count to 20–30% of baseline values is seen with fingolimod and siponimod; 45% of baseline values with ozanimod and 30–40% of baseline values with ponesimod. Treatment should be stopped if the lymphocyte count falls below 0.2×10^9/L, or if transaminases exceed five times the upper limit of normal(ULN) (or 3 times ULN with an elevated bilirubin).

For all S1P receptor modulators: A baseline ECG should be undertaken. Vaccination against VZV should be administered at least 1 month prior to initiation if there is no evidence of immunity. Pregnancy tests should be performed in all women and patients should be advised to take contraception during treatment. An ophthalmological examination should be performed in all patients at 3–4 months, then 6 months later, and then annually thereafter. BP, FBC, and LFTs should be reviewed at 1, 3, and 6 months, and then annually thereafter.

Siponimod: Patients should be genotyped for CYP2C9 prior to treatment. Patients with a CYP2C9*3*3 should not use siponimod, and those with a *2*3 or *1*3 genotype should only escalate to a maximum dose of 1 mg/day.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.44.
Interactions See Table 23.45.

Table 23.44 Pharmacokinetics of S1PR modulators

	Fingolimod	Ozanimod	Ponesimod	Siponimod
Bioavailability	93%	40–60% based on animal models	83.8%	84%
T_{max}	12–16 h	6–8 h	2–4 h	~4 h
Protein binding	>99%	98%	>99%	>99%
Metabolism	Hepatic predominantly by CYP4F2	Multiple mechanisms including hepatic and gut flora	Multiple CYP450 and non-CYP450 oxidative enzymes	Mainly CYP2C9, to a lesser degree CYP3A4
Pharmacologically active metabolites	Yes, strong	Yes, strong	No	No
Elimination half-life	6–9 days	21 h	33 h	30 h
Excretion	Urine 81%	Faeces 83% based on animal models	Faeces 60–80%	Faeces

Table 23.45 Interactions of S1PR modulators

Medications which alter S1PR modulator plasma levels	Pharmacodynamic interactions
No clinically relevant pharmacokinetic interactions are seen with ponesimod. **Levels decreased:** **Fingolimod:** CYP3A4 inducers, e.g. carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin, and St. John's Wort. **Ozanimod:** CYP2C8 inducers, e.g. rifampicin. MAOi, e.g. rasagline. **Siponimod:** CYP2C9 and 3A4 inducerse e.g. carbamazepine. **Levels increased:** **Fingolimod:** CYP3A4 inhibitors, e.g. ketoconaole. **Ozanimod:** CYP2C8 inhibitors, e.g. clopidogrel and gemfibrozil. **Siponimod:** CYP2C9 and 3A4 inhibitors, e.g. fluconazole.	**With amiodarone, β-blockers (i.e. atenolol), diltiazem, disopyramide, dronedarone, ketoconazole, and verapamil:** there is an increased risk of bradycardia. **With vaccinations:** immunizations will be less effective during treatment and for up to 6 weeks after treatment. Avoid live attenuated vaccines during and for 2 months after terminating treatment. **With antineoplastic, immunomodulatory, or immunosuppressive therapies:** avoid administration due to the risk of additive immune system effects.

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Phenytoin and fosphenytoin

Phenytoin is a widely used broad-spectrum ASM. Its main disadvantages are:

1. non-linear pharmacokinetics requiring regular monitoring of plasma levels;
2. high levels of pharmacokinetic interactions;
3. IV injections are associated with local toxic effects, due to the fact that phenytoin is water-insoluble and hence administered with alcohol and propylene glycol at a pH of 14;
4. long-term use is associated with dysmorphism, hirsutism, and hypertrichosis.

Fosphenytoin is a phenytoin prodrug, and hence the majority of its side effects and interactions are identical to phenytoin. Its main advantage over phenytoin is that it is water-soluble, and the concentrate for injection is at a physiological pH. This avoids the injection site toxicity of phenytoin and allows it to be given IM, if IV administration is not an option (although IM injection should not be used in the treatment of status, as T_{max} can take >24 h by this route of administration). It can be administered faster than phenytoin when given IV. It is only available by injection; hence its main use is in status epilepticus. Its main clinical effects are attributable to phenytoin, with which it shares many pharmacokinetic characteristics and side effects.

Uses

Licensed uses

In the UK/USA

1. Fosphenytoin.
    - *Epilepsy*: fosphenytoin is licensed for the treatment of tonic–clonic status epilepticus, for the prevention and treatment of seizures during or following neurosurgery (UK: and/or head trauma), and as a substitute for oral phenytoin if oral administration is not possible in individuals of all ages.

2. Phenytoin.
   - *Epilepsy*: phenytoin is licensed for the treatment of tonic–clonic seizures, focal-onset seizures with or without secondary generalization, and seizures occurring during or following neurosurgery (UK: and/or head injury) as a monotherapy or as an adjunct in individuals of all ages. Phenytoin as an injection or infusion is licensed for the treatment of tonic–clonic status epilepticus in individuals of all ages.

Off-label uses

- Trigeminal neuralgia.

Presentation

- *Trade names*: Cerebyx®, Dilantin®, Epanutin®, Phenytek®, and Sesquient®. Generics are available.
- *Formulations*: phenytoin is available as a capsule, an oral suspension, and a solution for IV injection. Capsule: 30 mg or 100 mg extended release. Oral suspension: 125 mg/5 mL. Solution for injection: 50 mg per millilitre in 2 mL and 5 mL single-dose vials. Fosphenytoin is available as IV/IM Injection. Injection: 50 mg phenytoin sodium, USP equivalents (PE)/mL available as: 10 mL single-dose injection vials, containing 500 mg PE, 2 mL single-dose injection vials, containing 100 mg PE.

Mechanism of action

The mechanism of action of phenytoin has not been fully established. It is thought that its main antiepileptic activity is via use-dependent blockade of voltage-sensitive sodium channels. It also regulates calmodulin and secondary messenger systems, enhances post-synaptic GABA-mediated inhibition, and inhibits the action of calcium channels presynaptically in order to block the release of neurotransmitters. Fosphenytoin has no known pharmacological activity prior to conversion to phenytoin.

Toxicity and side effects

- *Common—Dermatological*: rash can occur, and treatment should be stopped and only restarted if settling and mild in nature. If it reoccurs, then stop treatment permanently. Acne, hirsutism, hypertrichosis, and dysmorphism in the form of coarse facial features are common with long-term treatment. *Gastrointestinal*: anorexia, constipation, gingival hypertrophy, nausea, and vomiting. *Neurological*: headache, paraesthesia, sedation, tremor, and vertigo are common.

In addition, the following side effects have been reported with fosphenytoin use.

- *Common—Gastrointestinal*: dry mouth and taste disturbance. *Neurological*: dysarthria, tinnitus, visual disturbances, and weakness. *Psychiatric*: euphoria. *Dermatological*: bruising and pruritus.
- *Serious—Cardiovascular*: IV injection can cause hypotension, arrhythmias, and cardiovascular collapse, particularly if given too rapidly. BP and continuous cardiac monitoring are mandatory during IV administration. *Dermatological*: bullous, exfoliative, or purpuric dermatitis, acute generalized exanthematous pustulosis (AGEP), Stevens–Johnson

syndrome, and toxic epidermal necrolysis have rarely been reported. Purple glove syndrome: a purple discoloration and oedematous change to the skin, followed by subsequent necrosis. It is caused by phenytoin extravasation around the cannula site. There are no reports of purple glove syndrome with fosphenytoin use. *Gastrointestinal*: rarely, a toxic hepatitis can occur. *Haematological*: rarely aplastic anaemia, lymphoma, and pancytopenia have been reported. *Immunological*: DRESS, PAN, and SLE have rarely been reported. *Neurological*: rarely, irreversible cerebellar dysfunction and peripheral neuropathy can occur. *Psychiatric*: psychosis and suicidal ideation have been reported. *Renal*: interstitial nephritis is rare. *Respiratory*: pneumonitis and rapid IV administration can cause respiratory arrest.

Of note, less commonly, anaemia (often related to folic acid deficiency), osteomalacia, and weight gain can occur with long-term use.

Contraindications

- *Absolute*: hypersensitivity to phenytoin or its excipients.
- *Relative*: phenytoin is ineffective in the treatment of absence seizures, myoclonic jerks, childhood epileptic encephalopathy, and progressive myoclonic epilepsies. Phenytoin undergoes extensive hepatic metabolism and is renally excreted; hence, the dose should be lowered for hepatic and renal impairment. Monitoring of free non-protein-bound phenytoin plasma concentrations should guide dosing in these circumstances.

There is a cross-over with the rash associated with carbamazepine treatment (up to 50% of patients who had a skin rash with carbamazepine also developed one with phenytoin in small studies); hence phenytoin should be used with caution in individuals with a history of carbamazepine-induced rash.

Uses in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the probability of pharmacokinetic interactions is high.
- *Pregnancy*: There is demonstrable evidence of teratogenic risk to the human foetus. Phenytoin impairs endogenous vitamin K synthesis and hence increases the risk of haemorrhagic disease in the newborn. A prophylactic injection of vitamin K should be given. In addition, free phenytoin levels can reduce by 30–80% during pregnancy; hence doses may need to be increased. Use in patients during pregnancy involves weighing up the potential benefits and side effects (see Anti-seizure medications in young women, pp. 37–9).
- *Lactation*: it is not known if fosphenytoin is present in human breast milk, but phenytoin is. Plasma levels are <10% of those of the mothers. One small study did not show a statistically significant difference in IQ at 6 years old between children breastfed by mothers on phenytoin monotherapy vs. control. If used, infants should be monitored for potential side effects such as sedation and irritability. The infant should be switched to an alternative feeding regimen if these are identified.

Efficacy

1. *Fosphenytoin*: minimal evidence exists that looks specifically at fosphenytoin efficacy. One open-label study looked at the time to seizure cessation in patients with status epilepticus and found no significant difference between those given phenytoin or fosphenytoin. The maximal rate of fosphenytoin infusion is three times faster than that of phenytoin. However, this does not necessarily correlate with faster attainment of effective plasma phenytoin levels, which may be delayed as fosphenytoin needs to be converted by phosphatases to phenytoin.
2. *Phenytoin*: there are relatively little data from high-quality studies regarding efficacy of phenytoin, but to date no ASM has been shown to be superior. A 2001 Cochrane review demonstrated that phenytoin was effective at preventing post-traumatic seizures arising before 1 week but not after 1 week following brain injury. Hence administration of short-term phenytoin following moderate-to-severe head injuries to prevent early post-traumatic seizures is common. There is as yet little evidence to recommend routine prophylaxis of patients with cerebral space-occupying lesions or cerebral haemorrhage, thrombosis, and stroke. See Status epilepticus, p. 43, and seizures in neuro-oncology under Management of complications, p. 231 for discussion of the evidence in these scenarios.

Dosing and monitoring

Dosing

1. *Fosphenytoin*: doses are expressed as phenytoin sodium equivalent (PE). Fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg..
    - *For the treatment of status epilepticus*—age >18 years: start treatment with a bolus dose by IV infusion of 20 mg (PE)/kg at a rate of 100–150 mg (PE)/min. If necessary, may give an additional 5 to 10 mg PE/kg 10 min after loading dose for a maximum total loading dose of 30 mg PE/kg. Then give 4–7 mg (PE)/kg daily, divided into 1–2 doses. Administer the maintenance doses at a rate of 50–100 mg (PE)/min. Then adjust dosing according to clinical response and plasma phenytoin levels. BP, heart rate, and respiratory function monitoring are a requirement of IV administration.
    - *For prophylaxis or treatment of seizures associated with neurosurgery or head injury*—age >18 years: start treatment with a bolus dose by IM injection or IV infusion (at a rate of 100–150 mg (PE)/min) of 10–20 mg (PE)/kg. Then give 5 mg (PE)/kg in total daily, divided into 3 doses, by IM injection or IV infusion (at a rate of 50–100 mg (PE)/min). Then adjust dosing according to clinical response and plasma phenytoin levels.
    - *For use as a substitute to oral phenytoin*—age >18 years: use the same dose and frequency as oral phenytoin by IM injection or IV infusion (at a rate of 50–100 mg (PE)/min).
2. Phenytoin.
    - *For the treatment of all forms of epilepsy, except absence seizures*, age >18 years: start treatment at 4–7 mg/kg/day or 300–400 mg/day

in 1–2 divided doses. If given as a single dose, this should be given at night. The dose should be increased gradually, with plasma phenytoin monitoring, to a usual maintenance dose of 200–500 mg daily. Dosage changes should not occur faster than at 1-week intervals and should be ideally increased at 3- to 4-week intervals. There is no documented difference in the bioavailability of tablets vs. capsules. Oral doses should be taken with or after food.

- *For the treatment of status epilepticus*: a loading dose of 20 mg/kg is used and given by IV injection or infusion at a rate 25–50 mg/min. If necessary, may give an additional dose of 5 to 10 mg/kg 10 min after loading dose, maximum total loading dose 30 mg/kg. Then maintenance doses of 4–7 mg/kg/day (usually 300 to 400 mg/day) divided into 3 doses, orally or parenterally, and adjusted according to phenytoin concentration. BP and cardiac monitoring are a requirement of IV administration. A wide-bore cannula should be used with a large flush pre- and post-dose to minimize consequences of extravasation.

Monitoring

Hepatic and renal function should be assessed prior to initiating treatment and yearly thereafter. Measure folate and vitamin D levels on a regular basis.

***Therapeutic drug monitoring*:** Both ASMs should be monitored using phenytoin plasma levels: Optimum seizure control when used in monotherapy occurs at plasma concentrations of 10–20 mg/L. Trough samples should be taken. When phenytoin is used as maintenance therapy outside of status epilepticus, take the sample when steady state is reached at 1–3 weeks post-dose adjustment.

In settings where protein binding is affected, e.g. concomitant administration of phenylbutazone, salicylates, tolbutamide, and valproate, or when albumin concentration is altered, dosing is best guided through measurement of free non-protein-bound plasma concentrations

Pharmacokinetics and interactions

Pharmacokinetics

- *Fosphenytoin*: the bioavailability and T_{max} of fosphenytoin by the IM route is 100% and 0.5 h, respectively. Fosphenytoin undergoes hydrolysis to form phenytoin by phosphatase enzymes mostly present in the liver and red blood cells. The half-life for fosphenytoin conversion to phenytoin is 8–15 min. T_{max} for phenytoin following administration of fosphenytoin is 0.5–1 h by the IV route, and 1.5–4 h by the IM route; Phenytoin steady state is reached in 6–21 days. Fosphenytoin is 95–99% bound to protein. The rest of pharmacokinetics of fosphenytoin are as per phenytoin.
- *Phenytoin*: different formulations have slightly different T_{max} and bioavailability values. The oral bioavailability is on average >80%. T_{max} varies between 1.5 h and 3 h. Steady state is reached in 7–10 days. Ninety per cent of phenytoin is protein-bound, predominantly to albumin. Between 75% and 100% of phenytoin is metabolized hepatically. Metabolites are inactive. The major metabolite is 5-(p-hydroxyphenyl)-5-phenylhydantoin, the majority of which is

subsequently glucuronidated and eliminated via the renal system. Hydroxylation is mainly mediated by CYP2C9 and CYP2C19, which, alongside CYP1A2 and CYP3A4 isoenzymes, undergo autoinduction. This may necessitate an increase in dosage when steady state is reached. The phenytoin half-life increases at higher doses and in the absence of enzyme-inducing ASMs. The half-life averages 22 h. The majority of metabolites of phenytoin are excreted into the bile in GI tract, subsequently reabsorbed and then eliminated by the kidneys; <5% is eliminated as an unchanged drug.

Interactions

See Table 23.46. As a result of the magnitude of the interaction between diazoxide and phenytoin, whereby phenytoin plasma levels are decreased to almost non-detectable values, this drug combination can be considered contraindicated.

Table 23.46 Interactions of phenytoin and fosphenytoin

Medications which alter phenytoin plasma levels	Medications whose plasma levels are altered by phenytoin
Levels decreased: CYP3A4, CYP2C9, CYP2C19, and CYP1A2 inducers, e.g. rifampicin and St John's wort, Alcohol (chronic intake). Levels increased: acute alcohol intake, CYP3A4, CYP2C9, CYP2C19, and CYP1A2 inhibitors, e.g. cimetidine, indinavir, and voriconazole.	Levels decreased: CYP3A4, CYP2C9, CYP2C19, and CYP1A2 substrates, e.g. albendazole, amiodarone, and lamotrigine, oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban). Levels increased: chloramphenicol, clobazam (metabolite), and phenobarbital

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Recombinant Tissue Plasminogen Activators (rt-tPA)

Alteplase and tenecteplase are parenteral fibrinolytic agents, which are licensed for the management of acute ischaemic stroke. Alteplase was first approved for acute ischaemic stroke in the UK in the late 1990s. Tenecteplase is rapidly replacing the use of alteplase with its increased affinity and ease of use. Fibrinolytic therapy has the potential to restore cerebral blood flow and markedly improve neurological outcome when used in the first few h post-acute ischaemic stroke.

Uses

Licensed uses

In the UK/USA

(Tenecteplase has no licensed neurological uses)

- *Acute ischaemic stroke:* alteplase is licensed for the treatment of acute ischaemic stroke in individuals aged 16 years and older. In the UK the licensing states it should be used within 4.5 h of symptom onset, whilst in the USA it should be used within 3 h of symptom onset.

Off-label uses

- Alteplase has been used outside of the 3–4.5-h window in select cases of acute ischaemic stroke, e.g. basilar stroke. Tenecteplase has been used in the management of acute ischaemic stroke.

Mechanism of action

Alteplase (tPA) and tenecteplase (TNK) are recombinant tissue plasminogen activators (rt-PA), which convert plasminogen to plasmin. Plasmin is an enzyme that degrades fibrin clots. This acts to restore blood flow through an occluded artery. TNK is derived from tPA. It differs from tPA by three-point mutations resulting in replacement of three amino acids at the T, N, and K positions of tPA. Compared to alteplase, it is eightfold more potent at dissolving clots, has a 14-fold enhanced specificity to fibrin, has a longer half-life and an 80-fold higher resistance to plasminogen activator inhibitor 1.

Toxicity and side effects

- *Common—Cardiovascular*: hypotension. *Gastrointestinal*: nausea and vomiting. *Haematological*: iron deficiency anaemia. *Immunological*: allergic reaction, injection site reaction.
- *Serious—Cardiovascular*: recurrent ischaemia or angina, heart failure, reperfusion arrhythmias. *Gastrointestinal*: haemorrhage (occasionally major). *Immunological:* Angioedema. *Neurological*: intracranial haemorrhage. *Respiratory*: pulmonary oedema.

Contraindications

Contraindications shared by alteplase and tenecteplase:

- Absolute:
  1. Current intracranial haemorrhage
  2. Subarachnoid haemorrhage
  3. Active internal bleeding
  4. Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
  5. Presence of intracranial conditions that may increase the risk of bleeding (e.g. some neoplasms, arteriovenous malformations, or aneurysms)
  6. Bleeding diathesis
  7. Current severe uncontrolled hypertension
- Relative: In the following conditions, the risks of bleeding for all approved indications are increased and should be weighed against the anticipated benefits:
  1. Recent major surgery or procedure (e.g. coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels)
  2. Cerebrovascular disease
  3. Recent intracranial haemorrhage
  4. Recent gastrointestinal or genitourinary bleeding
  5. Recent trauma
  6. Hypertension: systolic BP above 175 mm Hg or diastolic BP above 110 mm Hg
  7. High likelihood of left heart thrombus, e.g. mitral stenosis with AF
  8. Acute pericarditis
  9. Subacute bacterial endocarditis
  10. Haemostatic defects including those secondary to severe hepatic or renal disease
  11. Significant hepatic dysfunction
  12. Pregnancy
  13. Diabetic haemorrhagic retinopathy, or other haemorrhagic ophthalmic conditions Septic thrombophlebitis or occluded AV cannula at the seriously infected site
  14. Advanced age
  15. Patients currently receiving anticoagulants (e.g. warfarin sodium)
  16. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

In the USA, the American Stroke Association recommends additional contraindications to alteplase use in the management of acute stroke when considered 3–4.5 h post-onset of symptoms:

1. Age >80 years,
2. Patients taking oral anticoagulants (irrespective of INR),
3. A baseline National Institutes of Health Stroke Scale (NIHSS) score of >25,
4. Ischaemic injury occupying more than one-third of the middle cerebral artery (MCA) territory,
5. Patients with both a prior stroke and diabetes.

Impaired renal function is not a contraindication for use of either rt-tPA. In an experienced stroke physician's hands, some of the contraindications listed may not be absolute in practice, and, in complex cases, careful consideration of the balance of risk and benefit is required.

Use in special populations

Elderly: No dosage adjustment is required, however caution is recommended in patients ≥ 75 years, as they are more likely to have an increased bleeding risk.

Pregnancy:

Alteplase: Its use may lead to premature separation of the placenta in the first 18 weeks of pregnancy. It additionally confers an increased risk of maternal haemorrhage and a theoretical risk of foetal haemorrhage throughout pregnancy. The American Heart Association (AHA) and American Stroke Association (ASA) guidelines recommend the use of IV tPA for moderate-to-severe strokes in pregnancy when the benefit justifies the potential risk to the foetus.

Tenecteplase: The FDA has issued a warning regarding TNK use in pregnancy. TNK has been shown to lead to maternal and embryo toxicity in rabbits given multiple (but not single) IV administrations. There are no adequate and well-controlled studies in pregnant women, and therefore, TNK should be administered only in instances where the potential benefits justify the potential risk to the foetus.

Lactation: There are no human studies of the effects of rt-tPA on the infants of breastfeeding mothers. Both are found in breastmilk; however they are large proteins and likely to be digested in the infant gastrointestinal tract. Given the lack of available data it would be reasonable to avoid breastfeeding during treatment.

Efficacy

Alteplase: Early trials of alteplase use within the first 3 h of symptom onset in acute ischaemic stroke demonstrated that patients were at least 30% more likely to have minimal or no disability at 3 months, when compared to placebo (NINDSr-tPA). The ECASS III RCT suggested that favourable outcomes could be obtained when alteplase was used up to 4.5 h post-symptom onset. However, other similar small studies suggested there was no benefit in giving alteplase after 3 h (ATLANTIS and ECASS II).

Ultimately, a much larger study, the IST-3 trial, was conducted to clarify whether alteplase should be used in situations where the benefit was uncertain, e.g. >3 h from onset, >80 years. It was a large (n = 3035, of whom 1617 patients were older than 80 years of age) randomized, open-label trial, which ascertained that patients thrombolysed within 6 h of symptom onset had improved functional outcomes, a benefit that extended to the population aged >80. However, no benefit was conferred with regards to mortality. Those who were thrombosed faced an increased number of deaths within the first 7 days (7% vs. 1%), while those who were not had a higher mortality rate between 7 days and 6 months.

In patients with large vessel occlusion stroke, the combination of mechanical thrombectomy along with intraoperative intra-arterial tPA administration has a trend towards achieving better functional outcomes and lower mortality rates, without any difference in postoperative haemorrhage rates. However, the existing quality of evidence is low, and the risk of bias is high. RCTs are warranted to provide a higher degree of certainty.

Tenecteplase: According to early clinical trials the safety and efficacy of TNK (0.4 mg/kg) is comparable to that of tPA. The Australian-TNK trial demonstrated a better 90-day neurological outcome in TNK treated patients, when compared to alteplase patients. Similarly, the EXTEND-IA TNK trial showed that TNK (0.25 mg/kg) before thrombectomy, was associated with a higher TICI (thrombolysis in cerebral infarction) perfusion score and functional outcomes, compared to alteplase, prior to thrombectomy, in patients with large vessel occlusion.

A recent systematic review and meta-analysis of all published RCTs compared the efficacy of tenecteplase and alteplase in relation to the following outcomes: modified Rankin Scale (mRS) 0–1, mRS 0–2, mortality, and symptomatic intracranial haemorrhage (sICH). Comparable rates of mRS 0–1 and 0–2 at 90 days were found between both agents. Studies included, however, did have heterogeneity in mRS 0–2 rates. Rates of mortality and symptomatic intracranial haemorrhage (sICH) rates were comparable in both treatment groups. There was no significant heterogeneity among included studies in either mortality or sICH rates. Analysis comparing dosing of tenecteplase (0.1, 0.25, 0.32, and 0.4 mg/kg) yielded no significant differences for any of the endpoints (mRS 0–1, mRS 0–2, sICH, and mortality) compared to alteplase.

Dosing and monitoring

Dosing

Alteplase: The total dose is 0.9 mg/kg (maximum 90 mg). The first 10% of the dose is given by IV injection over 60 seconds, and the remainder by IV infusion over 60 min.

Tenecteplase: TNK is administered intravenously as a single bolus. Different doses have been tested for acute ischaemic stroke in Caucasian adults, including 0.1, 0.25, 0.4, and 0.5 mg/kg. The AHA advocates the use of 0.25 mg/kg in acute ischaemic stroke, as available data does not suggest a significant advantage from higher doses. The maximum dose should not surpass 50 mg (10,000 units) in total.

Due to an increased haemorrhagic risk, antiplatelet and anticoagulant agents should not be started until at least 24 h after administration of either rt-tPA.

Monitoring

During and for up to 24 h following administration of rt-tPA BP should be monitored closely.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.47.

Alteplase undergoes extensive and rapid hepatic clearance. The half-life is 4–5 min. At 20 min <10% of the initial dose remains in the plasma.

Tenecteplase also undergoes extensive hepatic metabolism, however this is significantly slower than alteplase. There is biphasic elimination from the plasma, the initial half-life is 24 min, and the terminal half-life is 129 min.

Interactions See Table 23.47.

Table 23.47 rt-tPA inhibitors

Pharmacodynamic interactions
With ACE inhibitors: Increased risk of angioedema **With antiplatelets and anticoagulants:** increased risk of bleeding.

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Selective serotonin and noradrenaline reuptake inhibitors

SNRIs are a group of drugs most commonly used in the management of mood disorders. However, several of the SNRIs have also been demonstrated to have neurological applications. Three SNRIs (duloxetine, milnacipran, and venlafaxine) have been found to be effective in treating various forms of neuropathic pain. In addition, venlafaxine is used in the management of narcolepsy. Other SNRIs such as sibutramine have not been discussed further, given they are rarely used for neurological indications.

These drugs are generally very specific, only acting to increase the synaptic levels of 5-hydroxytryptamine (5HT) and noradrenaline (NA), with virtually no inhibition of monoamine oxidase. Duloxetine and venlafaxine are more potent inhibitors of serotonin uptake than NA, while milnacipran has a 3-fold higher inhibition of NA reuptake, compared to serotonin.

Uses

Licensed uses

In the UK/USA

1. *Duloxetine:* neuropathic pain—duloxetine is licensed for pain relief in diabetic neuropathy in adults.
2. *Milnacipran:* fibromyalgia—milnacipran is licensed for the treatment of fibromyalgia in individuals aged 18 years and older; it is not licensed for use in the UK.
3. *Venlafaxine*: venlafaxine is licensed for treatment of mood disorders in the UK and USA. There is no licensed neurological use in either country.

Off-label uses

Duloxetine: Migraine and other causes of peripheral neuropathy.
Venlafaxine: narcolepsy, diabetic neuropathy, migraine, and other causes of peripheral neuropathy.

Mechanism of action

- *Narcolepsy*: the mechanism of action of venlafaxine in the management of narcolepsy is unclear. Venlafaxine and other antidepressants may work through their combined noradrenergic and serotonergic activity. This may inhibit REM-on neurons in the brainstem, preventing spontaneous attacks of REM sleep.
- *Neuropathic pain*: SNRIs block 5HT and NA reuptake transporters, achieving analgesia in a similar fashion to TCAs. They have a narrower spectrum of activity than TCAs, which minimizes the extent of their side effect profile.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension, palpitations. *Dermatological*: flushing. *Gastrointestinal*: appetite change, constipation, dry mouth, nausea, vomiting, and weight change. *Neurological*: dizziness, headache, tremor. *Psychiatric*: abnormal dreams, insomnia.
- *Serious—Cardiovascular*: hypertensive crisis. *Dermatological*: Stevens–Johnson syndrome. Duloxetine has been reported to cause anaphylaxis and angio-oedema. *Metabolic*: rhabdomyolysis. *Neurological*: seizures. *Ophthalmological*: angle-closure glaucoma. *Psychiatric*: suicidal behaviour.

With venlafaxine: additional side effects to be aware of include:

- Serious—Cardiovascular: QT prolongation. Gastrointestinal: pancreatitis. Psychiatric: NMS.

NB. Withdraw gradually. Symptoms of withdrawal include anxiety, dizziness, headache, nausea, paraesthesiae, sleep disturbances, tremor, and vomiting. In patients treated with venlafaxine for narcolepsy, abrupt cessation of venlafaxine has been associated with status cataplecticus, i.e. recurrent attacks of cataplexy with little or no refractory period.

Contraindications

All SNRIs.

- *Absolute*: concomitant use of MAOIs.
- *Relative*: angle-closure glaucoma, bleeding disorders, cardiac disease, elderly, mania, seizures, and uncontrolled hypertension.

In addition:

1. Duloxetine.
    - *Absolute*: hepatic impairment and renal impairment eGFR <30 mL/min/1.73 m^2.
2. Milnacipran.
    - *Relative*: renal impairment eGFR <30 mL/min/1.73 m^2; reduce the dose by 50%. No dose adjustment is necessary for hepatic failure.
3. Venlafaxine.
    - *Absolute*: eGFR <10 mL/min/1.73 m^2.
    - *Relative*: eGFR 10–30 mL/min/1.73 m^2 (halve the dose) and hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustment is required in the elderly, although care with increasing doses is recommended.
- *Pregnancy*: there are no controlled data for use of SNRIs in pregnancy. There does not appear to be an increased risk of foetal congenital malformations. SSRIs have an increased risk of persistent pulmonary hypertension of the newborn and although this has not been reported in SNRIs, given their similarities this possibility should be considered. There have been individual reports of increased neonatal complications, including feeding difficulties, irritability, and respiratory and neurological complications such as hyperreflexia, hypo-/hypertonia, and seizures. It is advised that the SNRIs should only be given in pregnancy, particularly in the third trimester, if the benefit outweighs the risk.
- Lactation:
    1. *Duloxetine*: is present in breast milk, although the effects on the developing infant are unknown. There is a small risk of neonatal withdrawal syndrome with duloxetine. Duloxetine risk is acceptable to use during breastfeeding.
    2. *Milnacipran*: there are no studies available reporting the safety of milnacipran in breastfeeding. Levels in breastmilk are considered low and are not expected to cause adverse events in infants, however more data is required to make a strong recommendation. To be used with caution. Manufacturers advise to avoid in the absence of robust safety data.
    3. *Venlafaxine*: Venlafaxine and its metabolite *O*-desmethylvenlafaxine are both present in breast milk. No proven reports of side effects to date. Both the American Academy of Pediatricians and the National Institute of Health in the UK consider venlafaxine safe for breastfeeding.

Efficacy

1. *Duloxetine*: A recent review identified 18 trials, including 6407 participants in total, 2728 patients with diabetic neuropathy and

2249 with fibromyalgia. For a >50% reduction in pain over a 12-week period in diabetic neuropathy, the NNT was 5 (95% CI 4–7), and in fibromyalgia it was 8 (95% CI 4–21). One small high-quality trial found no effect from duloxetine in treating central neuropathic pain.

2. *Milnacipran*: a recent systematic review identified five RCTs, with a total of 4138 participants, comparing milnacipran to placebo for pain relief in fibromyalgia. Doses of 100 mg and 200 mg provided >30% reduction in pain to 40% of those treated, compared to 30% of participants in the placebo arm. The NNT was 8.6 (95% CI 6.3–14). Milnacipran has not been studied in other forms of neuropathic pain.
3. Venlafaxine.
   - *Narcolepsy*: the evidence for venlafaxine in the management of narcolepsy comes purely from case series evidence and expert consensus statements. In case series, symptoms of cataplexy, excessive daytime sleepiness, and hypnagogic hallucinations improved with the use of venlafaxine in the majority of subjects.
   - *Neuropathic pain*: a systematic review identified six studies investigating the effectiveness of venlafaxine in treating neuropathic pain. Three studies demonstrated that venlafaxine was superior to placebo in significantly reducing global pain relief measurements, with an NNT of 3.1 (95% CI 2.2–5.1). These studies included patients with post-mastectomy pain, painful polyneuropathy, and experimentally induced pain. Three other studies only reported mean data. Venlafaxine has not been adequately studied in other forms of neuropathic pain, including painful diabetic neuropathy, post-herpetic neuralgia, or central pain.

Dosing and monitoring

Dosing

1. *Duloxetine*: start treatment at 30 mg. Increase to 60 mg od after 1 week. Maximum dose 120 mg daily.
2. *Milnacipran*: start on day 1 with a single 12.5 mg dose; on days 2–3, administer 12.5 mg bd; on days 4–7, administer 25 mg bd; after day 7, administer 50 mg bd. Based on patient response, the dosage may be increased to 100 mg bd.
3. *Venlafaxine*: starting dose: 37.5 mg od. Increase the dose by 37.5–75 mg each week, as tolerated. Usual maintenance dose is 75–225 mg/day for neuropathic pain. In narcolepsy, maintenance doses of 150–375 mg have been used in case studies.

Monitoring

None is routinely required for duloxetine and milnacipran. Venlafaxine was found to cause a dose-related increase in BP, particularly with doses >200 mg. Controlling pre-existing hypertension before starting venlafaxine and routine BP monitoring thereafter is recommended.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.48.

Interactions See Table 23.49.

Table 23.48 Pharmacokinetics of SNRIs

	Duloxetine	Milnacipran	Venlafaxine
Main routes of administration	PO	PO	PO
Oral bioavailability	50%	85%	42%
T_{max}	6 h	2–4 h	5.5 h
Protein binding	95%	13%	30%
Time to steady state	3 days	2 days	3 days
Pharmacologically active metabolites	No	Yes, strong	Yes, strong
Elimination half-life	8–17 h	6–8 h	Standard: 3–7 h MR: 9–13 h
Metabolism	CYP1A2, CYP2D6	glucuronide conjugation	CYP2D6 metabolism forms *O*-desmethylvenlafaxine (ODV)
Excretion	As metabolites: urine 70%, faecal 20% Unchanged: urine <1%	Unchanged: urine >50%	As metabolites: urine 80% Unchanged urine 5%

MR, modified release; PO, oral.

Table 23.49 Interactions of SNRIs

Medications which alter duloxetine plasma levels	Pharmacodynamic interactions
Levels increased: duloxetine: ciprofloxacin and fluvoxamine; venlafaxine: clozapine and haloperidol	**With antiplatelets, anticoagulants, and NSAIDs:** increased risk of bleeding **With 5HT receptor agonists, e.g. SSRIs, TCAs, tramadol:** increased serotonergic side effects **With MAOIs/adrenaline/NA:** risk of hypertensive crisis. Do not start until at least 5 days after stopping duloxetine. **With atomoxetine:** increased seizure risk **With methylammonium:** increased risk of CNS toxicity

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Statins

Statins are a group of widely used lipid-regulating drugs that inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Statins have shown utility in the primary and secondary prevention of cardiovascular and cerebrovascular disease.

There are several statins of varying potencies available on the market. At present, atorvastatin, pravastatin, rosuvastatin, and simvastatin have been evaluated in the context of ischaemic stroke. No studies have compared the relative efficacies of the different statins in ischaemic stroke.

Uses

Licensed uses

In the UK/USA

Statins are licensed for the treatment of hypercholesterolaemia and prevention of cardiovascular events and stokes in individuals who have had or are at high risk of a cardiovascular event.

Off-label uses

Secondary prevention following ischaemic stroke.

Mechanism of action

All statins act by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway. This metabolic pathway mediates the hepatic production of cholesterol. This reduced hepatic cholesterol pool triggers increased expression of the low-density lipoprotein (LDL) receptor and subsequent lowering of plasma LDL-cholesterol (LDL-C). The *SATURN* trial has also demonstrated that high-dose atorvastatin and rosuvastatin can lead to atheroma regression. Statins have also been demonstrated to exert additional pleiotropic effects, such as improving/restoring endothelial function and anti-inflammatory effects. They may also reduce the chance of developing AF. Thus, statins may reduce occlusive thrombotic events, irrespective of the initial cholesterol concentration.

All statins are given orally in tablet form. They are typically given at night when peak cholesterol synthesis occurs. Little is known about IV administration of statins and their effects in the acute situation. However, a recent animal study that utilized IV rosuvastatin demonstrated protection from focal cerebral ischaemia for up to 4 h after a cerebrovascular event. Future studies will further investigate this route of administration.

Toxicity and side effects

Statin-induced muscular side effects, range from myalgia (reported in up to 13% of patients commenced on statin therapy) to rhabdomyolysis. Muscle-related side effects have been seen more commonly with lipophilic statins (simvastatin, atorvastatin), in comparison to those with a hydrophilic structure (pravastatin, rosuvastatin).

- *Common—dermatological*: pruritus and rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, vomiting. *Immunological*: allergic reaction. *Musculoskeletal*: muscle cramps, myalgia, and myopathy. *Neurological*: dizziness, headache, and paraesthesiae. *Respiratory*: bronchospasm.
- *Serious—gastrointestinal*: hepatic failure, hepatitis, and pancreatitis. *Immunological*: angio-oedema. *Musculoskeletal*: rhabdomyolysis.

Contraindications

- *Absolute*: hypersensitivity to the drug or its excipients. Active liver disease or unexplained persistent elevations of serum transaminases that are >3 times the upper limit of the reference range. Pregnancy and lactation. Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, and nefazodone). Acute porphyria.
- *Relative*: use statins with caution in those with risk factors for rhabdomyolysis or myopathy (personal or family history of muscle disorders, a high alcohol intake, renal impairment, hypothyroidism, and in the elderly). All statins should be used with caution in hepatic impairment.

Use in special populations

- *Elderly*: the elderly have a higher risk of rhabdomyolysis and myopathy, and thus statins should be used cautiously and titrated carefully.
- *Pregnancy*: statins are contraindicated in pregnancy and should be discontinued before conception, as congenital abnormalities have been reported and the reduction in cholesterol synthesis may affect foetal development. Thus, appropriate contraception is advised both during and for 28 days following cessation of treatment.
- *Lactation*: it is not known whether statins are present in breast milk. Manufacturers advise avoidance on the basis that they may disrupt infant lipid metabolism.

Efficacy

- *Atorvastatin*: the *SPARCL* (*S*troke *P*revention by *A*ggressive *R*eduction in *C*holesterol *L*evels) trial randomly assigned 4731 ambulatory patients with no known coronary heart disease (CHD) who had had a stroke or TIA within the preceding 6 months to treatment with either atorvastatin 80 mg/day or placebo. Atorvastatin was associated with a reduction in fatal or non-fatal stroke, as well as a significant reduction in all coronary events (5.2% vs. 8.6%).

- *Pitavastatin*: this newly developed statin is an HMG-CoA-reductase inhibitor indicated as an adjunctive therapy to diet in adults with primary hyperlipidaemia or mixed. The effect of pitavastatin on cardiovascular morbidity and mortality has not yet been evaluated. However, a recent multicentre prospective hospital-based cohort study found that pitavastatin 4 mg substantially reduced LDL-C levels and increased HDL-C levels in patients with dyslipidaemia. In this same study, the use of pitavastatin was associated with a low discontinuation rate, fewer adverse events, and an extremely small number of cases of new-onset diabetes. Another randomized comparison study, entitled the PATROL trial, compared pitavastatin, atorvastatin, and rosuvastatin and found that all three statins were equal in terms of safety and efficacy. A meta-analysis of randomized control studies likewise reported that pitavastatin was equivalent to simvastatin in both efficacy and safety. It is important to note that no studies to date have primarily analysed pitavastatin in ischaemic stroke.
- *Pravastatin*: in the CARE trial, pravastatin was shown to reduce the incidence of stroke in patients who were prescribed pravastatin after MI. Compared with placebo, pravastatin resulted in a 27% reduction in stroke or TIA (95% CI 4–44%; $p = 0.02$).
- *Rosuvastatin*: the JUPITER study was a double-blind RCT that investigated the use of rosuvastatin in the primary prevention of cardiovascular disease. The trial appraised 17,802 patients with no previous history of cardiovascular disease and low-normal LDL-C but an elevated high-sensitivity C-reactive protein (CRP) (hs-CRP) to either 20 mg rosuvastatin or placebo. hs-CRP is a biomarker of inflammation and has been shown to be an independent predictor of future vascular events (statin therapy has previously been shown to reduce hs-CRP levels). Rosuvastatin was shown to reduce LDL-C levels by 50% and reduce hs-CRP by 37%. Rates of stroke were found to be 0.18 and 0.34 per 100 person-years follow-up (48% relative risk reduction) in the rosuvastatin and placebo groups, respectively (hazard ratio 0.52, 95% CI 0.34–0.79).
- *Simvastatin*: the *HPS* trial (*H*eart *P*rotection *S*tudy) enrolled 3280 adults with cerebrovascular disease who had previous non-disabling ischaemic stroke, TIA, and/or a history of carotid endarterectomy or angioplasty, but excluded patients who had had a stroke within 6 months. An additional 17,256 subjects with other occlusive arterial disease or diabetes were also enrolled. Patients were allocated to either 40 mg simvastatin or placebo and monitored over a 5-year treatment period. Simvastatin treatment was associated with a significant reduction in all first stroke, compared with placebo (4.3% vs. 5.7%), reflecting a 28% RRR in ischaemic strokes ($p < 0.0001$).

Statin therapy in acute ischaemic stroke

National recommendations, including NICE guidelines, advise that statins should be commenced 48 h after the onset of ischaemic stroke.

The 48-h delay before initiation of statins arose due to theoretical concerns of an increased risk of haemorrhagic conversion if used hyperacutely. This is based on the SPARCL trial of 2006, which suggested an increased risk of haemorrhagic stroke in those taking 80 mg/day of atorvastatin, in comparison to placebo (2.3% vs. 1.4%; $p = 0.002$). However, it is important to note that: (1) the benefits of atorvastatin in preventing further ischaemic strokes far outweighed the increased risk of haemorrhagic stroke; (2) post-hoc analysis demonstrated that increased risk was primarily observed in elderly men with a history of haemorrhagic stroke; (3) further meta-analyses have not shown any increased risk of ICH with statin use, following ischaemia; and (4) there is no direct evidence of harm in giving early statins in acute stroke.

Recent studies suggest that patients may benefit from statin treatment from stroke onset. A meta-analysis of 27 studies by Chroinin *et al*. demonstrated that patients who were on a statin prior to the onset of symptoms had improved functional outcome at 90 days (OR 1.41, 95% CI 1.29–1.56; $p < 0.001$). A significant reduction in mortality was reported at both 90 days (OR 0.71, 95% CI 0.62–0.82; $p < 0.001$) and at 12 months (OR 0.80, 95% CI 0.67−0.95; $p = 0.01$). Furthermore, Flint *et al*. demonstrated, in a retrospective analysis, that withdrawal of statin therapy following ischaemic stroke was associated with a significantly greater risk of death (hazard ratio 2.5, 95% CI 2.1–2.9; $p < 0.001$). The ASSORT trial aimed to assess the efficacy of early (within 24 h) and delayed (7 days after admission) commencement of statin after stroke in 11 hospitals in Japan and did not show the superiority of early treatment. However, it is noted that 44% of the subjects in this study had lacunar infarctions, which are regarded as pathophysiologically distant from strokes associated with atheromatous disease.

In conclusion, given the significant benefit demonstrated in these studies, patients already on statin therapy should continue their usual regimen, without interruption, following an acute stroke. For patients not previously on a statin, no unifying conclusion exists on immediate vs. delayed administration of statins after acute stroke, with further studies required to assess if there is any added benefit from starting therapy *de novo* at stroke onset.

Statin therapy following intracerebral haemorrhage

It is unclear whether statins should be initiated in patients at high risk of ICH. Post-hoc analyses from the SPARCL trial and other studies suggest that statins may increase the risk of ICH in some patient groups, typically men who have already suffered from ICH. Having said this, several medium-sized meta-analyses have demonstrated that patients on statins prior to ICH have better outcomes and reduced mortality at 90 days. Furthermore, ICH survivors do not appear to be at increased risk of recurrence. A decision model created by Westover *et al*. suggested that, on the basis of the available evidence, statins should be avoided in those with previous lobar ICH and used only with caution in those with previous ‘deep’ ICH.

Ribe *et al*. specifically set out to investigate whether statin treatment increased the likelihood of ICH in prior stroke patients. They found that the risk of ICH was similar between those with prior ICH regardless of statin use and reduced by half in those with prior stroke and statin use.

Overall, given the current evidence, it appears sensible to exercise caution when utilizing statin therapy in those with previous ICH, particularly those of lobar location.

Dosing

- *Simvastatin*: following acute ischaemic stroke or TIA start treatment at 40 mg od.
- *Atorvastatin*: following acute ischaemic stroke or TIA 80 mg od.
- *Pitavastatin:* following acute ischaemic stroke or TIA 1–4 mg od.
- *Pravastatin*: following acute ischaemic stroke or TIA 80 mg od.
- *Rosuvastatin*: following acute ischaemic stroke or TIA 20 mg od.

Monitoring

Caution should be exercised in patients with predisposing factors for rhabdomyolysis. In order to establish a reference baseline value, a creatine kinase (CK) level may be measured before starting a statin in the following situations: elderly (age ≥65 years), female gender, renal impairment, uncontrolled hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with a statin or fibrate and alcohol abuse. If muscle pain, weakness, or cramps occur, while a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 times the upper limits of normal), treatment should be stopped. If symptoms resolve and CK levels return to normal, then reintroduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring. Those who experience sensitivity to one statin do not necessarily experience adverse effects with other statins.

LFTs should be measured before commencing treatment and be repeated at 3 and 12 months (unless there are clinical symptoms or signs of hepatotoxicity).

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.50.
Interactions See Table 23.51.

Table 23.50 Pharmacokinetics of statins

	Atorvastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Main routes of administration	PO	PO	PO	PO	PO
Oral bioavailability	30%	51%	34%	>10%	60–80%
T_{max}	2–3 h	1 h	0.9–1.6h	3–5h	1.3–2.4h
Protein binding	>98%	>99%	50%	90%	78–87%
Solubility	Fat-soluble	Fat-soluble	Water-soluble	Water-soluble	Fat-soluble
Pharmacologically active metabolites	Yes	No	No	Yes (minor)	Yes
Elimination half-life	15–30 h	12 h	1.3–2.8h	20.82h	2–3h
Metabolism	CYP3A4	Glucuronidation, CYP2C9, CYP2C8	Sulfation	CYP2C9, 2C19	CYP3A4
Elimination	96% faeces, 2% urine	75% faeces, 2% renal	70% faeces, 20% urine	90% faeces, 10% urine	80% faeces, 13% urine

Table 23.51 Interactions of statins

Medications which alter statin plasma levels	Medications whose plasma levels are altered by statins	Pharmacodynamic interactions
Levels decreased: CYP3A4/ CYP2C9 inducers, e.g. carbamazepine, efavirenz, rifampicin, St John's wort, etc.	Levels increased: atorvastatin, coumarins, digoxin, ethinylestradiol, midazolam, and norethisterone	With other agents that may cause myopathy, e.g. antiretrovirals, ciclosporin, corticosteroids, fibrates, etc.: increased risk of myopathy
Levels increased: CYP3A4/ CYP2C9 inhibitors, e.g. indinavir, fluconazole, clarithromycin, and erythromycin		With antipsychotics, SSRIs, zidovudine, colchicine, and lithium: increased risk of rhabdomyolysis

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Thienopyridines, including clopidogrel, prasugrel, and ticagrelor

The thienopyridines are a group of prodrugs, which are metabolized to active metabolites that irreversibly inhibit the $P2Y_{12}$ platelet receptor. This reduces platelet activation and aggregation. The three main drugs used in neurological practice are clopidogrel, prasugrel, and ticagrelor. Clopidogrel has been in use in the UK and the USA since the 1990s. This group of drugs are used in combination with aspirin for dual-antiplatelet therapy in the prevention of transient ischaemic attack and ischaemic stroke.

Uses

Licensed uses

Clopidogrel:

In the UK/ USA

- *MI and stroke prevention after recent MI, stroke, or established peripheral artery disease*: clopidogrel is licensed for the secondary prevention of thrombotic cerebrovascular disease, in individuals aged 18 years and older, who have recently suffered ischaemic stroke.

In the UK only

- *Atherothrombotic and thromboembolic event prevention in AF*: clopidogrel is licensed for prevention for patients with one vascular risk factor where aspirin alone is not sufficient and oral anticoagulation with a vitamin K antagonist is not tolerated, in individuals aged 18 years and older.

Prasugrel and Ticagrelor have no licensed neurological uses in either the UK or USA.

Off-label uses

- Prasugrel and Ticagrelor can be used to reduce the risk of stroke following acute ischaemic stroke or high-risk transient attack.

Mechanism of action

Thienopyridine metabolism by esterase enzymes produce active metabolites which irreversibly bind to the active site of the platelet $P2Y_{12}$ receptor resulting in the subsequent inhibition of platelet aggregation. Prasugrel requires fewer metabolic steps than clopidogrel and this reduces the influence of CYP2C19 polymorphisms. This means it may prevent ischaemic stroke in more patients than clopidogrel.

Toxicity and side effects

- ***Common to clopidogrel, ticagrelor and prasugrel:***
- *Common: Cardiovascular*: Hypotension and syncope. *Gastrointestinal:* Abdominal pain, dyspepsia, diarrhoea, nausea. *Haematological:* Bleeding—predominantly minor (epistaxis, gastrointestinal, urinary,

bruising, post-procedural, traumatic). *Neurological:* Dizziness, headache, vertigo.

- *Serious: Dermatological:* Bullous dermatitis (toxic epidermal necrolysis), Stevens–Johnson syndrome, erythema multiforme, AGEP, drug-induced hypersensitivity syndrome, DRESS. *Gastrointestinal:* Acute liver failure and hepatitis. *Haematological:* Severe bleeding (e.g. intracranial haemorrhage, retroperitoneal haemorrhage). *Immunological:* Hypersensitivity, including angioedema, thrombotic thrombocytopenic purpura (TTP).
- ***Specific to ticagrelor:***
- *Common: Metabolic:* Hyperuricemia and gout. *Respiratory:* Dyspnoea.

Contraindications

- *Absolute*: Hypersensitivity to the medication or its excipients. Severe hepatic impairment and active significant bleeding,
- *Relative*: History of intracranial haemorrhage and co-administration with strong CYP3A4 inhibitors. Moderate hepatic impairment.
- No dose adjustment is required in mild hepatic impairment or renal impairment of any severity.

Use in special populations

- *Elderly*: The elderly are at a higher risk of gastrointestinal bleeding, and this must be considered when commencing thienopyridines in this population.
- *Pregnancy*:

Clopidogrel: Animal studies do not suggest harmful effects to the foetus; however, there is limited experience from use in humans, and hence the manufacturer advises avoidance in pregnancy.

Ticagrelor: Should not be used in patients who are trying to conceive or who are pregnant. Ticagrelor has demonstrated teratogenic potential in animal studies.

Prasugrel: Animal studies have shown no harm. However, it should only be used if any potential risk to the foetus is outweighed by the expected benefits for the mother.

- *Lactation*: Clopidogrel and ticagrelor are excreted in breastmilk. Manufacturers advise avoidance in nursing mothers. It is unknown whether prasugrel is excreted in breastmilk, therefore it is not recommended for use in nursing mothers.

Efficacy

Clopidogrel: The CHANCE trial demonstrated that the 90-day risk of stroke was reduced with dual-antiplatelet therapy (DAPT), consisting of a clopidogrel 300 mg loading dose on day 1 followed by 75 mg daily in addition to aspirin 75 mg daily for 21 days, when started within 24 h of minor ischaemic stroke or high-risk TIA. The POINT trial demonstrated that among patients with minor ischaemic stroke or high-risk TIA, a short course (90 days) of DAPT of clopidogrel 600 mg loading dose followed by 75 mg/day plus aspirin 50–325 mg/day initiated within 12 h reduced the risk of major ischaemic events compared to aspirin alone, without significantly increasing the risk of major haemorrhage. The SAMMPRIS trial

demonstrated that, in patients with recent transient ischaemic attack or stroke due to intracranial arterial stenosis, medical management (aspirin at 325 mg per day and clopidogrel at 75 mg per day for 90 days) was superior to percutaneous transluminal angioplasty and stenting.
DAPT for more than 90 days has been shown to increase the risk of haemorrhage without a significant improvement in the risk of ischaemic infarcts when compared to antiplatelet monotherapy.

Clopidogrel may be less effective in patients with CYP2C19 loss-of-function mutations. The CHANCE-2 trial identified that ticagrelor and aspirin were more effective than clopidogrel and aspirin in these patients.

Prasugrel:

Stroke: Prasugrel is not commonly used in the secondary prophylaxis of stroke due to concerns that it may lead to an increased rate of haemorrhagic adverse events compared to clopidogrel, as indicated in the TRITON-TIMI38 study. This study used 10 mg/day as a maintenance dose. PRASTRO-I and II investigated the use of prasugrel 2.5 or 3.75 mg/day in the secondary prevention of non-cardioembolic ischaemic stroke in Japanese patients. Sub-analysis of the PRASTRO-I study by stroke subtype identified that prasugrel was as effective as clopidogrel in patients with large-artery atherosclerosis and small-vessel occlusion. In patients with thrombotic stroke, the composite incidence of ischaemic stroke, MI, and death from other vascular causes was 3.5% in the prasugrel group and 4.3% in the clopidogrel group. Prasugrel may be preferable for treating recurrent cases that have had a stroke whilst on treatment with clopidogrel as some patients may exhibit resistance to clopidogrel. It has been reported that the risk of thrombotic events is lower in patients treated with prasugrel than in those treated with clopidogrel among poor metabolizers due to CYP2C19 polymorphisms.

Ticagrelor: Several studies have found that adding ticagrelor to aspirin reduces the risk of recurrent stroke and other major vascular events compared to aspirin alone in patients with minor ischaemic stroke or high-risk TIA. A network meta-analysis of five randomized trials with over 22,000 patients found that treatment with both ticagrelor with aspirin and clopidogrel with aspirin was superior to aspirin alone in preventing recurrent stroke or death up to 90 days following acute stroke, however, was no significant difference in efficacy between the ticagrelor- and clopidogrel-treated groups.

Dosing and monitoring

Dosing

Clopidogrel: For stroke prevention in the setting of a recent MI, stroke, or peripheral artery disease, start treatment at 75 mg once daily without a loading dose.

Prasugrel: There is no recommended dose for the prevention of stroke. Studies undertaken for the indication of acute coronary syndrome included a loading dose followed by a maintenance dose (a single 60-mg oral loading dose, followed by 10 mg orally once daily. The dosing was reduced to 5 mg for patients with body weight <60 kg). Trials in stroke prevention have used 3.75 mg/day without a loading dose.

Ticagrelor: To prevent acute ischaemic stroke, initiate treatment with a 180 mg loading dose (two tablets of 90 mg) followed by 90 mg twice daily for up to 30 days.

Monitoring

Full blood count monitoring can be used for patients at risk of bleeding.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.52.
Interactions See Table 23.53.

Table 23.52 Pharmacokinetics of thienopyridines

	Clopidogrel	Prasugrel	Ticagrelor
Bioavailability	50%	86%	90%
T_{max}	1–2 h	1 h	1 h
Protein binding	98%	99%	88%
Metabolism	Hepatic: CYP2C19	Hepatic: CYP2B6 and CYP3A4	Hepatic: CYP3A4
Pharmacologically active metabolites	Yes	Yes	Yes
Elimination half-life	8 h (active metabolite)	7 h	8–12 h
Excretion	Primarily urine	Primarily faeces	Primarily faeces

Table 23.53 Interactions of thienopyridines

Pharmacodynamic interactions
With aspirin, coumarins, dipyridamole, heparins, iloprost, NSAIDs, and prasugrel: increased risk of bleeding
With carbamazepine, chloramphenicol, ciprofloxacin, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, oxcarbazepine, and voriconazole: possible reduction of antiplatelet effect
With cimetidine, omeprazole, and esomeprazole: reduction in antiplatelet effect (although current evidence is conflicting)

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Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are dibenzoazepine derivatives of chlorpromazine. The first TCA, imipramine was used in 1955. Due to their unfavourable side effect profile, they have largely been replaced by newer antidepressants for the treatment of depression, e.g. SSRIs and SNRIs. However, TCAs still have an important role in the treatment of several neurological conditions, including headache, insomnia, narcolepsy, and neuropathic pain. Notably, the analgesic and sedative effects desired in neurological conditions are often independent of their antidepressant effect. In general, the time to achieve an analgesic effect is days, compared to weeks for an antidepressant effect, and the effective dosage required is typically lower for many of the neurological indications.

There are a large number of TCAs. Only those used in the management of neurological conditions are discussed here further. These comprise clomipramine and imipramine, which preferentially inhibit 5HT reuptake; desipramine and nortriptyline, which preferentially inhibit NA reuptake; and amitriptyline, which produces a balanced inhibition of NA and 5HT reuptake. In addition to classification in terms of their pharmacological action, TCAs can also be grouped by their chemical structure. Amitriptyline, clomipramine, and imipramine are tertiary amines, whereas desipramine and nortriptyline are demethylation products of imipramine and amitriptyline, respectively, and are hence termed secondary amines.

Which tricyclic antidepressant to use?

Amitriptyline has been used in most trials for neuropathic pain and therefore is often the first-line choice as it has the largest evidence base. If amitriptyline fails due to intolerable side effects, NICE guidance recommends switching to an alternative TCA such as nortriptyline. All TCAs have a similar side effect profile however, nortriptyline is generally better tolerated than amitriptyline, particularly in the elderly, as it causes less sedation and dry mouth. However, if one TCA is ineffective, rather than not tolerated, then NICE recommends a trial of a drug from a different class, e.g. an anti-seizure medication such as gabapentin.

Uses

Licensed uses

In the UK/USA

1. *Amitriptyline* is licensed for a wide range of psychiatric disorders, as well as neuropathic pain. It is indicated for prophylactic treatment of chronic tension-type headaches and migraines in adults.
2. *Clomipramine* is licensed as an adjunct in the management of cataplexy associated with narcolepsy in individuals aged 18 years and older in the UK. In the USA, clomipramine has no licensed neurological indications.
3. *Desipramine* is licensed for a wide range of psychiatric disorders. There is no licensed neurological use, and desipramine is no longer marketed in the UK.
4. *Imipramine* is licensed for a wide range of psychiatric disorders, as well as childhood enuresis. There is no licensed neurological use.
5. *Nortriptyline* is licensed for a wide range of psychiatric disorders. There are no licensed neurological uses.

Off-label uses

1. *Amitriptyline*: insomnia and MOH.
2. *Clomipramine/desipramine/imipramine*: migraine prophylaxis and neuropathic pain. Desipramine may improve the core symptoms of ADHD.
3. *Nortriptyline*: neuropathic pain and prophylaxis of migraine and tension-type headache (TTH).

Mechanism of action

Most TCAs work as serotonin (5HT) and norepinephrine (NA) reuptake inhibitors, increasing synaptic levels of these neurotransmitters. They also have a broad but variable spectrum of activity at multiple other receptors, including action as antagonists at α1-adrenergic receptors, NMDA receptors, H1 and H2 histamine receptors, and muscarinic acetylcholine receptors, and as agonists at sigma receptors. Actions at these sites contribute to their significant side effect profile. Most TCAs also potently inhibit sodium channels and L-type calcium channels, which causes cardiotoxicity and a high mortality rate in overdose.

- *Headache/narcolepsy/neuropathic pain*: it is unclear how TCAs reduce the severity of headache and neuropathic pain, or reduce the incidence of cataplexy. Their action is likely to be multimodal by interaction in the neurotransmitter pathways. In neuropathic pain, they may modulate neurotransmission of the descending pain pathways and thus inhibit nociceptive signals, while, in headache, they are believed to reduce the cortical spreading depression seen in migraine.
- *Insomnia*: the sedating effect of amitriptyline is predominantly mediated by its antihistamine action at the H1 receptor. It may also promote sleep by antagonistic effects at 5HT2 and muscarinic receptors. Treatment of underlying anxiety and depression may also contribute, as these are frequently associated with insomnia, although doses used in insomnia are much reduced, compared to doses used routinely in the treatment of these conditions.

Toxicity and side effects

- *Common—antimuscarinic*: blurred vision, constipation, dry mouth, urinary retention. *Neurological*: dizziness, drowsiness, paraesthesiae. *Psychiatric* (particularly in the elderly): agitation, anxiety, confusion, irritability, and sleep disturbance.
- *Serious—cardiovascular*: arrhythmia (including QT interval prolongation), heart block, risk of cardiotoxicity, and death in overdose. *Gastrointestinal*: paralytic ileus. *Haematological*: desipramine has been reported to cause agranulocytosis. *Neurological*: convulsions, NMS.

Contraindications

- *Absolute*: immediate recovery from MI, heart block, arrhythmias, acute mania, acute porphyria. Desipramine is contraindicated in patients with a family history of sudden cardiac death.
- *Relative*: TCAs reduce the seizure threshold and can exacerbate prostatic hypertrophy, urinary retention, and angle-closure glaucoma. They should be avoided with tramadol, due to the risk of serotonin syndrome (rare), and monoamine oxidase inhibitors. TCAs should be started with care in patients with phaeochromocytoma, hyperthyroidism, diabetes, and severe liver disease. No dose alteration is required in hepatic or renal impairment.

Use in special populations

- *Elderly*: the elderly are more susceptible to anticholinergic systemic and cognitive side effects, which may lead to confusion, delirium, and increased risk of falls. They may benefit from lower dosing regimens.
- *Pregnancy*: No teratogenic effects were observed in animal studies and there have been no proven reported side effects when used in pregnancy. However, there remains limited evidence. Use if the benefit outweighs the risk.
- *Lactation*: TCAs are present in low quantities in breast milk. There is limited evidence for neonatal side effects with any of the TCAs, but given the potential for serious reactions, a decision about discontinuing the medication or nursing should be considered.

Efficacy

1. ***Amitriptyline.***
    - *Headache*: amitriptyline has been shown to be consistently effective in *migraine* prophylaxis but, due to its side effect profile, is a second-line agent. In a systematic analysis of four RCTs, amitriptyline was found to be more effective than placebo in all the trials. It significantly reduced the number of headache days by 6.9 for TTH and 1.4 for migraine. In *TTH*, amitriptyline is a first-line agent, with one RCT (*n* = 203) demonstrating that headache severity was significantly reduced in 38% of patients on amitriptyline, compared to 29% with placebo. In *MOH*, amitriptyline has been shown to be effective in open-label studies, but superiority over placebo has not been shown in RCTs. In an RCT, it was shown to non-significantly reduce headache, when compared to placebo (45% vs. 28%; p = 0.3).
    - *Insomnia*: no controlled studies have been undertaken. Evidence for use of amitriptyline in insomnia is predominantly based on expert

consensus guidelines and known sedative side effects identified from studies of its action in mood disorders.
  - *Neuropathic pain*: the effectiveness of amitriptyline in neuropathic pain has been established through a number of systematic reviews. In one systematic review, involving ten studies with a total of 588 patients suffering from diabetic neuropathic pain, post-herpetic neuralgia, or cancer neuropathic pain, the NNT was 3 (95% CI 2.5–4.2). A further systematic review evaluated the use of amitriptyline in the management of diabetic neuropathy, fibromyalgia, post-herpetic neuralgia, and post-stroke pain in a total of 687 participants over eight studies. The NNT was 4.6 (95% CI 3.6–6.6).

2. ***Clomipramine***.
   - *Narcolepsy*: evidence for the use of clomipramine in the treatment of cataplexy is mostly based on case studies. One small comparative cross-over study compared clomipramine with fluvoxamine in the management of narcolepsy and demonstrated, that out of 11 patients treated with clomipramine, ten of these patients demonstrated some improvement in the frequency of cataplexy attacks. In four of these patients, attacks of cataplexy ceased altogether, and there was a >50% reduction in cataplexy attacks in a further three patients. Sleep paralysis was also dramatically reduced; however, there was little improvement in excessive daytime sleepiness. Numbers were insufficient to suggest which out of clomipramine and fluvoxamine was the more effective drug. In 2021, a systemic review of the literature in Europe was conducted, which recommended clomipramine as a strong medication for cataplexy in adults.
   - *Neuropathic pain*: the efficacy of clomipramine has only been studied in small clinical trials. One such study of 19 patients showed a significant reduction in all patients' reports of neuropathic pain in diabetic neuropathy, with a 39% reduction in pain score, compared to placebo ($p < 0.05$).
3. ***Desipramine*:** a systematic review identified two studies, involving 100 patients, demonstrating that desipramine offers pain relief to patients with post-herpetic neuralgia. The NNT was 2.6 (95% CI 1.9–4.5).
4. ***Imipramine*:** evidence for the effect of imipramine in treating neuropathic pain has been summarized in a systematic review. This included three studies investigating the use of imipramine in 114 patients with painful diabetic neuropathy. The NNT was 2.2 (95% CI 1.7–3.22).
5. ***Nortriptyline*.**
   - *Headache*: there is no trial evidence to support the use of nortriptyline in the prophylaxis of migraine or TTH. However, it is the active metabolite of amitriptyline and hence thought to be similarly effective. In addition, when compared to amitriptyline, it has a more favourable side effect profile, with less sedation and weight gain.
   - *Neuropathic pain*: two cross-over studies have looked at nortriptyline in the treatment of post-herpetic neuralgia. One study compared the efficacy of nortriptyline to amitriptyline and found both to be

equally effective, providing 21 of the 33 participants with moderate pain relief. Another study of 71 patients compared desipramine or nortriptyline treatment to placebo for painful herpetic neuralgia. The individual TCAs were not analysed separately, but a significant reduction in pain was found overall with both treatments. The NNT was 4.0 (95% CI 2.6–8.9).

Dosing and monitoring

Dosing

- *Neuropathic pain*: is the same for all TCAs—starting dose: 10 mg at night. Increase by 10–25 mg every 3–7 days. Maximum dose 150 mg daily. Greater than 75 mg requires specialist supervision. Trial for 6–8 weeks, with at least 2 weeks at the maximum tolerated dose.

1. Amitriptyline.

- *Headache*: start treatment at 10 mg, given at night. This can be increased at weekly/fortnightly intervals by 10–25 mg to 50–100 mg at night, according to response. The maximum recommended dose is 150 mg for migraine and 50 mg in MOH.
- *Insomnia*: 10 mg or 25 mg given at night.

2. Clomipramine.

- *Narcolepsy*: start treatment at 10 mg od at night; this can be increased up to a maximum of 75 mg/day in divided or single doses gradually over thes course of 2 weeks. Low doses (≤20 mg) are often effective.

3. Nortriptyline.

- *Headache*: the starting dose is 10–25 mg at night, increased at weekly/fortnightly intervals by 10–25 mg, according to response. The therapeutic dose ranges from 10 mg to 150 mg daily. It can be given in divided doses.

Monitoring

None routinely required. In patients who have, or are at risk of, cardiovascular disease, consider baseline ECG/repeat ECG at dose changes. TCAs should be withdrawn gradually to avoid discontinuation side effects.

Table 23.54 Pharmacokinetics of TCAs

	Amitriptyline	Clomipramine	Desipramine	Imipramine	Nortriptyline
Main routes of administration	PO	PO	PO	PO	PO
Oral bioavailability	30–60%	50%	73–92%	94–96%	51%
T_{max}	4 h	2–6 h	2–6 h	2–6 h	5 h
Protein binding	96%	97–98%	73–92%	86%	93–95%

(Continued)

Table 23.54 (*Contd.*)

	Amitriptyline	Clomipramine	Desipramine	Imipramine	Nortriptyline
Time to steady state	3–8 days	3 weeks	19 days	19 days	10–14 days
Pharmacologically active metabolites	Yes, strong	Yes, strong	No	Yes, strong	Yes, strong
Elimination half-life	30 h	21–36 h	15–24 h	20 h	8–28 h
Metabolism	CYP2D6, CYP2C19	CYP2D6, CYP2C19	CYP2D6	CYP2D6, CYP2C19	CYP2D6
Excretion	Urine 95%	Urine 60%, faeces 30%	Urine 70%	urine 80%, faeces 20%	Urine 90%, faeces 10%

PO, oral.

Most TCAs undergo extensive hepatic first-pass metabolism, a large volume of distribution, and binding to plasma proteins. All TCAs are metabolized by P450 2D6. Seven to 10% of Caucasians are poor metabolizers. Any drug that interacts with P450 2D6 will alter the plasma concentration of TCAs.

Table 23.55 Interactions of TCAs

Medications which alter TCA plasma levels	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenobarbital, phenytoin, St John's wort Levels of sublingual medications, e.g. nitrates, are reduced due to poor absorption with dry mouth **Levels increased:** CYP2D6 inhibitors, e.g. antipsychotics and SSRIs	**With CNS depressants, e.g. alcohol, antihistamines, anxiolytics, and opioids:** enhanced sedative side effects **With methylthioninium, rasagiline, selegiline, and tramadol:** increased CNS side effects **With MAOI:** TCAs should not be started until 2–3 weeks after stopping an MAOI. MAOIs should not be started for 1–2 weeks after stopping a TCA **With antiarrhythmics, e.g. amiodarone, disopyramide, flecainide, sotalol; antimicrobials, e.g. moxifloxacin; antipsychotics, e.g. droperidol and pimozide; antivirals, e.g. saquinavir; and sympathomimetics:** increased risk of arrhythmias **With hypotensive agents:** increased risk of low BP **With antimuscarinic agents, e.g. antihistamines:** increased antimuscarinic side effects **With lithium:** increased toxicity

Pharmacokinetics and interactions

Pharmacokinetics: See Table 23.54.
Interactions: See Table 23.55.

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Triptans

The triptans are a large group of 5HT agonists, which have been shown to be highly effective in treating migraine and cluster headache. There are many triptans available, the advantages and disadvantages for which are outlined in Table 23.56.

Uses

Licensed uses

In the UK

- Migraine.

1. *Almotriptan* is licensed for the acute management of migraine (with or without aura) in individuals aged 18 years and older. In the USA

- Migraine.

1. *Almotriptan* is licensed in the acute management of migraine (with or without aura) in individuals aged 12 years and older who experience migraine lasting ≥4 h without treatment.

In the UK/USA

(Licensing is the same.)

- Migraine.

Table 23.56 Advantages and disadvantages of different triptan medications

	Preparations	Advantages	Disadvantages
Almotriptan	12.5 mg tablet	Highest bioavailability, lower incidence of chest pain	Renally excreted—needs dose reduction in renal impairment
Eletriptan	40 mg tablet	Most effective triptan	Has the most side effects. Not recommended for use in the >65s
Frovatriptan	2.5 mg tablet	Licensed for MAM, prolonged therapeutic effect (long half-life), possible better cardiovascular risk profile	Potential for visual disturbance. Not recommended for use in the >65s
Naratriptan	2.5 mg tablet	Licensed for MAM, better side effect profile	Slow onset of action, dose reduction in renal impairment. Not recommended for use in >65s
Rizatriptan	10 mg dispersible/ standard tablet	Dispersible tablet useful if nausea and vomiting during attacks	Dose reduction in renal impairment. Contraindicated in patients with severe hepatic or renal insufficiency
Sumatriptan	Oral tablet: 50 mgNasal spray: 5–20 mg SC injection: 6 mg	Most supportive evidence. Multiple routes of administration	Not licensed for use in the >65s
Zolmitriptan	Dispersible and standard tablet and nasal spray: 2.5 mg	Rapidly absorbed, licensed for adolescents, licensed for MAM	Not licensed for use in the >65s

*MAM: Menstrual-associated migraine

1. *Eletriptan* is licensed for the acute treatment of migraine (with or without aura) in individuals aged between 18 and 65 years of age.
2. *Frovatriptan* is licensed for the acute treatment of migraine (with or without aura) in individuals aged between 18 and 65 years of age.
3. *Naratriptan* is licensed for the acute treatment of migraine (with or without aura) in individuals aged between 18 and 65 years of age.

4. *Rizatriptan* is licensed for the acute management of migraine (with or without aura) in individuals aged 18 years and older (UK) and in individuals aged 6 years and older (USA).
5. *Sumatriptan* is licensed for use in the acute management of migraine (with or without aura) in individuals aged between 18 and 65 years. The SC injection is also licensed for use in the acute management of cluster headache.
6. *Zolmitriptan* is licensed for the acute management of migraine (with or without aura) in individuals aged between 18 and 65 years of age.

Off-label uses

Cluster headache.

Mechanism of action

Triptans are believed to have a variety of targets in the CNS. They are thought to cause cerebral vasoconstriction, most likely via activation of $5HT_{1B}$ receptors present on the smooth cells of the cerebral vasculature. They are also believed to act on $5HT_{1D}$ receptors present on trigeminal neurons, thus preventing the release of vasoactive, pro-inflammatory neuropeptides. They may also block the transmission of nociceptive signals from reaching the thalamus through activity at $5HT_{1D}$ receptors in the dorsal horn.

Toxicity and side effects

- *Common—cardiac*: the 'triptan sensations' are a constellation of adverse effects commonly experienced with triptan administration. They include flushing, dizziness, and transient throat and chest tightness.
- *Dermatological*: injection site reactions include bleeding, bruising, and erythema. *Gastrointestinal*: epistaxis (nasal spray), diarrhoea, nausea, unpleasant taste. *Neurological*: paraesthesiae may be experienced as part of the triptan sensations.
- *Serious—cardiac*: arrhythmias, myocardial ischaemia, stroke. *Gastrointestinal*: bowel obstruction, deranged LFTs, mesenteric ischaemia. *Immunological*: anaphylaxis.

Contraindications

- *Absolute*: history of coronary vasospasm, ischaemic heart disease, MI, hepatic or renal failure, severe hypertension, stroke, or TIA. Hypersensitivity to triptans or any of their components is also a contraindication. Triptans should not be used in hemiplegic or basilar migraines.
- *Relative*: triptans can be used in elderly patients but are unlicensed and should be used with caution.

Use in special populations

- *Elderly*: triptans should be used with caution in the elderly, due to the increased prevalence of cardiovascular disease in this group. Almotriptan and rizatriptan, although efficacy and safety are not well established, can be used in individuals aged ≥65 years. Eletriptan, frovatriptan, naratriptan, sumatriptan, and zolmitriptan are not licensed for patients aged ≥65 years, due to a lack of efficacy and tolerability data.

- *Pregnancy*: in animal studies, almotriptan, naratriptan, and rizatriptan have been shown to cause foetal harm. There are limited data on the safety of the other triptans. No studies have evaluated rates of neurodevelopmental outcomes following *in-utero* triptan exposure. However, a recent study found that triptans may be associated with an increased risk of spontaneous abortion (aOR 1.63, 95% CI 1.34–1.98). The current recommendation is that the triptans should only be used in pregnancy if the expected benefit outweighs the risk of harm. The largest experience comes with sumatriptan and for this reason it may be preferred over other triptans if they are needed during pregnancy.
- *Lactation*: the triptans are all present in breast milk, but in quantities thought to be too small to be harmful. The poor oral bioavailability of triptans also reduces infant exposure. The current advice is that breastfeeding should be stopped until 24 h (12 h for sumatriptan) after the last dose was taken.

Efficacy

1. *Triptans (as a class):* A recent systematic review and meta-analysis found that triptans were significantly associated with reduced pain at 2 h and 1 day. Another review similarly confirmed the efficacy of triptans in migraine relief, resulting in equivalent or better outcomes compared with non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), and acetaminophen.
2. *Almotriptan: migraine*—in a randomized, double-blind study of almotriptan (6.25 mg and 12.5 mg) vs. placebo, both doses of almotriptan were found to be more effective than placebo at reducing the severity of attacks at 2 h (number of attacks relieved 60% and 70% vs. 38%, respectively; $p < 0.001$), and less than one-third of patients had headache recurrence in 24 h. Almotriptan was also well tolerated, with no significant difference in adverse effects between treatment and placebo groups. The 12.5 mg dose was found to be the most efficacious, with few additional adverse effects, compared with the lower dose.
3. *Eletriptan: migraine*—20 mg, 40 mg, and 80 mg doses were found to be superior to placebo at reducing headache severity at 2 h in several RCTs. Eletriptan 20 mg has a similar efficacy to sumatriptan 100 mg, while the higher doses 40 mg and 80 mg were found to be superior to sumatriptan 100 mg at reducing headache severity at 2 h and at maintaining a sustained response at 24 h. The cost-effectiveness of the 40 mg dose was felt to be equivalent to sumatriptan 50 mg or 100 mg. It is generally well tolerated, with commonly reported side effects including nausea, drowsiness, and dizziness (similar to other triptans). The 80 mg dose had a greater rate of adverse events than sumatriptan, while the other doses (20 mg and 40 mg) produced a comparable rate of adverse events to sumatriptan.
4. *Frovatriptan: migraine*—there have been several RCTs comparing frovatriptan 2.5 mg with placebo in migraine. All have demonstrated a clear benefit of frovatriptan. Response rates for frovatriptan have

ranged from 37% to 53%, compared with 21–34% with placebo. Patients were significantly more likely to be pain-free with frovatriptan, compared with placebo (9–19% vs. 2–6%, respectively). In comparisons with almotriptan and rizatriptan, frovatriptan was significantly less likely to result in headache recurrence at 48 h (27% for frovatriptan vs. 49% for other triptans; $p < 0.001$). Frovatriptan was generally well tolerated, with only 1% of patients stopping the drug because of adverse effects. Side effects were similar to other triptans and included dizziness, fatigue, and numbness.

5. *Naratriptan: migraine*—2.5 mg and 1 mg have been shown to be superior to placebo in several RCTs. In one trial, headache relief at 4 h was reported in 60% of patients taking 2.5 mg of naratriptan, compared with 50% for 1 mg and 34% for placebo (2.5 mg and 1 mg vs. placebo, $p < 0.05$). The efficacy of naratriptan is measured at 4 h due to its longer onset of action. Naratriptan 2.5 mg has been shown to be less effective than sumatriptan 50 mg or 100 mg but has fewer side effects. It has the lowest rate of migraine recurrence of the triptans (excluding frovatriptan). An advantage of naratriptan is its tolerability, with a similar side effect profile to placebo.
6. *Rizatriptan: migraine*—a Cochrane review of rizatriptan in acute migraine found that both the 5 mg and 10 mg doses were superior to placebo for all endpoints. For headache reduction at 2 h, the NNT for 5 mg was 3.9 (3.3–4.7), and for 10 mg 2.7 (2.4–2.9). A dose–response relationship was demonstrated, with the 10 mg dose showing greater efficacy than 5 mg. Compared with other triptans, rizatriptan is the second most effective at reducing headache severity at 2 h (after eletriptan).
7. *Sumatriptan: migraine*—a Cochrane review of the use of oral sumatriptan in migraine found that both the 25 mg and 50 mg doses of sumatriptan were superior to placebo in achieving a pain-free state at 2 h. The NNT was 6.1. The 100 mg dose was superior to both placebo and the lesser doses, reducing pain from moderate/severe to nil at 2 h in 32% of patients, compared with 11% for placebo. SC sumatriptan is sometimes preferred in the acute management of migraine, due to delayed gastric emptying and nausea and vomiting. A Cochrane review of SC sumatriptan found it to be superior to placebo for all outcomes. 59% of patients were pain-free at 2 h after a single 6 mg dose of sumatriptan, compared with 15% with placebo. It is also more effective than the oral equivalent but associated with a higher incidence of side effects. Intranasal sumatriptan has a quicker onset of action than the oral equivalent and fewer side effects.

Cluster headache—SC sumatriptan has been shown in randomized, placebo-controlled trials to be effective at reducing cluster headache pain at 30 min in about 75% of patients. Sumatriptan nasal spray is also effective in cluster headache. In a Cochrane review of triptans in cluster headache, the NNT with SC sumatriptan 6 mg for headache freedom at 15 min was 3.3.

8. *Zolmitriptan*: oral zolmitriptan has been shown to be more effective than placebo in a number of RCTs. In one trial comparing zolmitriptan with placebo, all doses of zolmitriptan were more effective than

placebo at reducing migraine severity at 2 h (53–67% vs. 34%, respectively; $p < 0.001$). Complete headache resolution was more likely with the higher doses of zolmitriptan (≥2.5 mg). The higher doses were associated with a higher rate of adverse events, but there were no reports of serious side effects. In trials comparing triptans, zolmitriptan 5 mg had a similar efficacy to sumatriptan 100 mg but was more effective than the lower doses of sumatriptan (25 mg and 50 mg). The dispersible tablets are useful in patients who are unable to take oral tablets because of nausea and vomiting, but there is no evidence that they work faster than the standard tablets. A Cochrane review concluded that zolmitriptan nasal spray in cluster headache was more effective than placebo at achieving pain freedom at 15 min (NNT 11, 6.4–49) but was less effective than SC sumatriptan.

Dosing and monitoring

Dosing

1. *Almotriptan*: a single dose of 12.5 mg should be given at the beginning of the migraine. If the headache recurs, a repeat dose can be given after 2 h. The maximum dose of 25 mg should not be exceeded within 24 h.
2. *Eletriptan*: 40 mg of eletriptan should be given at the beginning of headache onset. If headache continues, then a repeat 40 mg dose can be give 2 h after the initial dose. No more than 80 mg should be given in 24 h. Some patients may require an initial dose of 80 mg.
3. *Frovatriptan*: 2.5 mg should be given as soon as possible after the headache has started. If it recurs, a repeat dose can be given 2 h after the initial dose. No more than 5 mg should be given in 24 h.

For MAM, 2.5 mg should be started bd 2 days before the onset of menstruation and should be continued for a total of 6 days.

4. *Naratriptan*: 2.5 mg should be given as early as possible at the onset of headache. If headache recurs, a repeat dose can be given at least 4 h after the initial dose. If there is no response to the first dose, a repeat dose should not be given.

For MAM, 1 mg should be started bd 2 days before the onset of menstruation and continued for 5 days.

5. *Rizatriptan*: 10 mg should be given as soon as possible after the onset of headache. A repeat dose can be given at least 2 h after the initial dose if headache recurs. A second dose should not be given if there is no response to the first dose. The maximum dose in 24 h is 20 mg in the UK and 30 mg in the USA. If the patient is also taking propranolol, both the dose given to terminate and the maximum dose in 24 h should be halved.
6. *Sumatriptan—oral*. UK: the initial dose is 50 mg. This can be repeated at 2 h if there is some response to the first dose but the pain recurs. Some patients may require an initial dose of 100 mg. The maximum dose in 24 h is 300 mg. USA: an initial dose of 25 mg is recommended, with a maximum dose in 24 h of 200 mg. *SC*: for the SC route, 6 mg should be given for both migraine and cluster headache. This dose can be repeated after 1 h if the headache returns; no more than 12 mg should be given in 24 h. *Intranasal*: the dose is typically a single dose of 5–20 mg, repeated at 1 h if there is headache recurrence. No more than 40 mg should be given intranasally in 24 h.

7. *Zolmitriptan*: 2.5 mg should be given as soon as possible after the onset of headache. A repeat dose can be given 2 h after the initial dose if headache recurs. Some patients may require an initial dose of 5 mg. A second dose should not be given if there is no response to the first dose. The maximum dose in 24 h is 10 mg.

For MAM, 2.5 mg should be started bd to tds 2 days before the onset of menstruation and should be continued for 7 days (5 days after the start of menses).

With the nasal spray, one spray of 2.5 mg or 5 mg should be given into one nostril and should only be repeated after 2 h if headache recurs. The maximum dose is 10 mg in 24 h.

If the patient is also taking cimetidine, the maximum dose in 24 h is 5 mg.

Monitoring

Patients should be monitored for cardiac adverse effects, notably chest/throat tightness. If severe, triptans should be discontinued. If there are risk factors for ischaemic heart disease, an ECG should be considered before commencement.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.57.
Interactions See Table 23.58.

Table 23.57 Pharmacodynamics of triptans

	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Main routes of administration	PO	PO	PO	PO	PO	IN/PO/SC	IN/PO
Bioavailability	~70%	50%	20% in men, 30% in women	70%	40–45%	16% IN14% PO 97% SC	40% PO100% IN
T_{max}	1–3 h	0.75–1.5 h (2.8 h in migraine)	2–4 h	2–3 h (3–4 h in migraine)	1–2.5 h	1.5 h IN, 2 h PO, 25 min SC	3 h IN, 1.5–3 h PO
Protein binding	35%	85%	15%	28–31%	14%	14–21%	25%
Pharmacologically active metabolites	No	Yes, weak	Yes, weak	No	No	No	Yes, strong
Elimination half-life	3.5 h	4 h	26 h	6 h	2–3 h	2 h	2.5–3 h

IN, intranasal; PO, oral; SC, subcutaneous.

Table 23.58 Interactions of triptans

Medications which alter triptan plasma levels	Pharmacodynamic interactions
Levels increased: Almotriptan: azole antifungals, fluoxetine, ritonavir, verapamil Eletriptan: macrolide antibiotics, ritonavir Frovatriptan: oral contraceptives, propranolol Rizatriptan: propranolol Zolmitriptan: cimetidine, moclobemide, quinolone antibiotics **Levels decreased:** Frovatriptan: ergotamine	**With ergot alkaloids:** triptans should not be given within 24 h of receiving this class of compounds; increased risk of vasospasm. **With metoclopramide and SSRIs/SNRIs:** avoid concomitant use due to risk of serotonin syndrome **With MAOIs:** increased risk of toxicity; avoid for 2 weeks after MAOIs stopped

As a rule, the triptans undergo hepatic metabolism, are eliminated mainly by the renal system, and do not display induction of liver enzymes. Eletriptan and frovatriptan are exceptions—10% and 36% renally excreted, respectively. Almotriptan, naratriptan, sumatriptan, and zolmitriptan are not affected by food ingestion. The peak concentration of eletriptan is increased 20–30% with a high-fat meal. The time to peak of frovatriptan and rizatriptan is delayed by 1 h if given with food, but there is no effect on bioavailability.

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Typical antipsychotics

Typical antipsychotics are characterized by their propensity to cause extrapyramidal side effects. This gave rise to the name 'neuroleptics', meaning to 'seize the neuron'. In addition to the treatment of psychosis, these agents are used to treat severe tics, chorea, and behavioural disturbances associated with late-stage neurodegenerative disease such as dementia.

Uses

Licensed uses

In the UK/USA

- Tic disorders.

1. *Haloperidol*: is licensed for the treatment of severe tics and TS in individuals aged 3 years and older (UK), and 18 years and older (USA).

In the UK

- *Chorea*.

1. *Haloperidol*: Treatment of mild-to-moderate chorea in Huntington's disease, when other medicinal products are ineffective or not tolerated.

In the USA

- Tic disorders.

1. *Pimozide*: is licensed for the treatment of motor and phonic tics in TS in individuals who have not responded adequately to first-line therapy in individuals aged 12 years and older.

Pimozide is used in the management of psychotic disorders but has no licensed neurological use in the UK.

Off-label uses

1. *Haloperidol*: chorea (USA).
2. *Sulpiride*: chorea, tics, and TS. Sulpiride is not available in the USA.

Mechanism of action

Their action in TS and other tic disorders is thought to be the result of dopamine (D2) receptor antagonism. A lower affinity for H1 histaminergic and $\alpha2$-adrenergic receptors means these drugs cause less sedation, orthostatic hypotension, and weight gain than atypical antipsychotics. There is, however, a greater incidence of extrapyramidal side effects.

Toxicity and side effects

- *Common—Cardiovascular*: orthostatic hypotension. *Dermatological*: rash. *Endocrine*: hyperprolactinaemia and menstrual disorder. *Gastrointestinal*: constipation, dry mouth, nausea, vomiting, and weight gain. *Neurological*: dizziness, extrapyramidal symptoms (tardive dyskinesia and parkinsonism), insomnia, and sedation. *Urological*: erectile dysfunction, urinary retention.
- *Serious—Cardiovascular*: prolonged QT and venous thromboembolism (VTE). *Neurological*: NMS. *Respiratory*: bronchospasm.

Contraindications

- *Absolute*: hypersensitivity to drug or its excipients, prolonged QT, and co-administration with medications known to prolong the QT interval (e.g. TCAs). Haloperidol should also be avoided in CNS depression, PD, and other lesions of the basal ganglia.
- *Relative*: epilepsy (reduction in seizure threshold). Caution should be taken in hepatic and renal impairment. Start with small doses and increase slowly.

Use in special populations

- *Elderly*: no dosage alteration is routinely recommended; however, the elderly are more prone to orthostatic hypotension, and trials of antipsychotics in elderly patients with dementia have suggested that there is an increased incidence of cerebrovascular events.
- *Pregnancy*: adverse events have been noted in animal studies; there are no controlled human studies. Increased risk of congenital malformations has been reported in this group, although there are likely to be confounding factors. Neonates born to mothers taking antipsychotics may exhibit extrapyramidal side effects or withdrawal. Typical antipsychotics should only be used in pregnancy if the benefits outweigh the risks.
- *Lactation*: all of the typical antipsychotics mentioned are excreted in breast milk; the manufacturers recommend avoidance by nursing mothers.

Efficacy

1. *Haloperidol*: a double-blind, placebo-controlled RCT ($n = 57$) established that both haloperidol and pimozide were effective in controlling tic disorders. Due to similar efficacy and better tolerability, pimozide is often used first-line. Greater than 70% of tic suppression can be anticipated in approximately two-thirds of patients with either of these agents.
2. *Pimozide*: a Cochrane review of six RCTs found pimozide to be more effective than placebo, slightly less effective than haloperidol, but also associated with fewer side effects. It was as effective as risperidone, with no significant difference between side effect profiles.
3. *Sulpiride*: short-term sulpiride treatment for TS in children and adolescents was assessed over 6 weeks in a recent open-label prospective trial ($n = 189$). The trial reported a significant reduction in vocal (64%) and motor (49%) tics and in the total Yale Global Tic Severity Score (59%) score ($p < 0.05$). In addition to its efficacy in tic disorders, small studies have suggested that its mood-stabilizing and antidepressant effects may also be useful in the management of co-morbid obsessive-compulsive disorder.

Dosing and monitoring

Dosing

1. *Haloperidol*: start treatment at 0.25–0.5 mg/day in two divided doses, and increase gradually, as required/tolerated, to a usual maintenance

dose of 0.5–3 mg/day in 2–3 divided doses. The maximum recommended dose is 6 mg.

2. *Pimozide*: start treatment at 1–2 mg/day in divided doses. Increase by 1 mg every other day, as required/tolerated, to a usual maintenance dose of 6–8 mg/day. The maximum recommended dose is 10 mg/day.
3. *Sulpiride*: start treatment at 50–100 mg/day and increase every 2–4 weeks by 100–200 mg, as required/tolerated. The usual maintenance dose is 100–400 mg bd. The maximum recommended dose is 2 g.

Table 23.59 Pharmacokinetics of typical antipsychotics

	Haloperidol	Pimozide	Sulpiride
Main routes of administration	IM, IV, PO	PO	PO
Oral bioavailability	60%	50%	25–40%
T_{max}	2–6 h	6–8 h	2–6 h
Protein binding	92%	99%	40%
Metabolism	Hepatic CYP3A4	Hepatic CYP3A4, CYP1A2, CYP2D6	Minimal metabolism
Pharmacologically active metabolites	No	Undetermined	No
Elimination half-life	18 h	55 h	6–8 h
Excretion	Urine (30%), faeces (20%)	Urine	95% urine and faeces unchanged

Table 23.60 Interactions of typical antipsychotics

Medications which alter typical antipsychotic* plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 and CYP2D6 inducers. **Levels increased:** CYP3A4 and CYP2D6 inhibitors (dependent on method of metabolism; see pharmacokinetics inTable 23.59)	**With CNS depressants, e.g. alcohol:** enhanced sedative effects **With agents known to prolong QTc, e.g. chlorpromazine and macrolide antibiotics:** increased risk of ventricular arrhythmia **With other antipsychotics (e.g. atypical)/tetrabenazine:** may increase the risk of extrapyramidal side effects **With antihypertensive agents:** increased risk of hypotension

* Haloperidol and pimozide.

Monitoring

An ECG should be performed at baseline. Monitor BMI, BP, FBC, glucose, and thyroid, renal, and liver function, as well as lipid panels, on a regular basis.

Pharmacokinetics and interactions

Pharmacokinetics: See Table 23.59.
Interactions: See Table 23.60.

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VMAT2 inhibitors, including deutetrabenazine, tetrabenazine, and valbenazine

Vesicular monoamine transporter type 2 inhibitors (VMAT2) act by depleting dopamine and other neurotransmitters at nerve terminals. Tetrabenazine has been used for the treatment of chorea in Huntingson's disease (HD) since the early 1970s. It is effective, but carries the risk of side effects such as parkinsonism, sedation, and depression. Deutetrabenazine and valbenazine are newer agents, licensed by the FDA in 2017 for the treatment of tardive dyskinesia. Although there have been no head-to-head trials they may have a lower incidence of side effects than tetrabenazine.

Uses

Licensed uses

In the UK

Chorea/Tardive dyskinesia:

Tetrabenazine is licensed for the treatment of Huntington's chorea in individuals aged 18 years and older. It is also licensed for the treatment of other hyperkinetic movement disorders associated with organic nervous system conditions, e.g. chorea, hemiballismus, and tardive dyskinesia.

Deutrabenazine and valbenazine are not available in the UK.

In the USA

Huntington's chorea/Tardive dyskinesia:

Deutetrabenazine and tetrabenazine are licensed for the treatment of chorea in Huntington's disease and tardive dyskinesia in individuals ages 18 years and older.

Off-label uses

- Tics and TS

Mechanism of action

The VMAT2 inhibitors are reversible inhibitors of type 2 vesicular monoamine transporters (VMAT2). These transporters are found on vesicles containing monoamine neurotransmitters, including dopamine, at nerve terminals. Inhibition prevents monoamine (primarily dopamine, but also serotonin and noradrenaline) uptake into these vesicles, preventing storage and release, resulting in overall depletion of monoamines by degradation within the cytoplasm. Part of the activity of VMAT2 inhibitors may also be mediated by inhibition of post-synaptic dopamine receptors. Deutetrabenazine differs from tetrabenazine in that deuterium replaces specific hydrogen atoms, which slows its metabolism allowing for twice daily dosing. Like tetrabenazine its metabolites have several off-target effects on dopamine and serotonin receptors, the implications of which are unclear. Valbenazine is the valine ester of the alpha-dihydrotetrabenazine isomer, an agent with specific inhibition of VMAT2 inhibitors. Its metabolism is slow, supporting once daily dosing.

Toxicity and side effects

Most side effects are short-lived and are alleviated by lowering the dose.

- *Common—Gastrointestinal*: nausea, elevated liver enzymes, and weight gain (can be beneficial in HD patients where increased energy expenditure results in weight loss). *Neurological*: akathisia, falls, headache, and sedation. *Endocrine*: hyperprolactinaemia.
- *Serious—Cardiovascular*: QTc prolongation and syncope. *Neurological*: acute dystonic reactions, neuroleptic malignant syndrome, parkinsonism (more likely to occur in older patients). *Psychiatric*: depression (more likely to occur in younger patients), suicidal ideation, and suicide. *Respiratory*: aspiration pneumonia.

Contraindications

- *Absolute*: hypersensitivity to the VMAT2 inhibitor or its excipients. Concomitant use (or use within the previous 14 days) of MAOIs, and concomitant use (or use within the previous 20 days) of reserpine. History of prolactin-dependent tumours (e.g. breast and pituitary), actively suicidal, parkinsonism, phaeochromocytoma, and breastfeeding are also contraindications. Valbenazine should not be used in severe renal disease.
- *Relative*: Depression or history of suicidality (repeated assessment of depressive symptoms is advised in patients taking VMAT-2 inhibitors). Patients with long QT syndrome or at risk of it. No dosage alteration is required in mild or moderate renal disease. Deutetrabenaine has not been trialled in severe renal failure, although metabolism is mainly mediated by the hepatic CYP450 system. Use with caution in this patient group. No dose alterations are required for tetrabenazine in severe renal disease.
- *Hepatic impairment:*

Deutetrabenazine/Tetrabenazine—in mild and moderate hepatic impairment, halve the initial dose, and up-titrate the dose slowly in the smallest increments. Patients with severe hepatic impairment have not been studied; therefore, additional caution is advised in these patients.

Valbenazine—reduce the dose and titrate up with caution in patients with moderate-to-severe hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustment is routinely required; however, the elderly are more prone to Parkinsonian-like side effects and hence should be monitored with caution.
- *Pregnancy*: there are little data on the use of VMAT2 inhibitors in pregnancy. Tetrabenazine does cross the placenta. In animal models there was an increase in the rate of stillbirths with tetrabenazine hence the manufacturers recommend avoiding treatment, if possible.
- *Lactation*: similarly, there are little data with regards use of VMAT2 inhibitors whilst breastfeeding. Several of the VMAT2 inhibitors have been identified in breastmilk, hence the manufacturers recommend avoiding breastfeeding whilst taking them.

Efficacy

Deutetrabenazine:

Tardive dyskinesia—Two double-blind, placebo-controlled trials, AIM-TD and ARM-TD investigated the safety and efficacy of deutetrabenazine for the treatment of tardive dyskinesia. In the AIM-TD study the abnormal involuntary movements score (AIMS) improved by –3.3 points in the largest dose treatment group of 36 mg/day, compared to –1.4 points in the placebo group ($p = 0.001$). ARM-TD also showed a significant improvement in the AIMS score when compared to placebo. There were low rates of psychiatric adverse events, which were similar in number to placebo.

Huntington's disease associated chorea—The First-HD study was a double-blind, placebo-controlled study that investigated the effect of deutetrabenazine vs. placebo in the management of chorea in patients with HD. The mean maximal chorea score improved by –2.5 units in the treatment arm when compared to the placebo arm ($p < 0.001$). Treatment success, as defined by the Clinical Global Impression of change score, occurred in 42% of patients in the deutetrabenazine group compared to 13% in the placebo group ($p = 0.002$).

Tetrabenazine:

Tardive dyskinesia—There have been no randomized controlled trials investigating the use of tetrabenazine in the treatment of tardive dyskinesia, although several early open-label, retrospective studies have drawn positive conclusions about its efficacy for this disorder.

Huntington 's disease-associated chorea—TETRA-HD was a 12-week randomized controlled trial ($n = 84$), undertaken by the Huntington Study Group. They found a significant reduction of the Unified Huntington's Disease Rating Scale (UHDRS) score of 3.5 points with tetrabenazine (TBZ), compared to placebo (95% CI 5.2–1.9; $p < 0.0001$). There was also a significant benefit in ratings of clinical global improvement ($p = 0.0074$). There were five serious adverse events reported, including suicide and restlessness/suicidal ideation. No overall improvement in functional scores was reported in this study, with some suggestion of functional decline in some measures. However, later analysis of these data, alongside unpublished data from CARE-HD, concluded that tetrabenazine does not appear to have a negative effect on function and cognition, both of which are likely to occur on treatment due to the natural history of the disorder.

A retrospective study, published in 2018, of over 4000 HD patients, 542 of whom were treated with tetrabenazine, found that treatment was not associated with an increased risk of depression or suicidality when compared with patients not treated with tetrabenazine.

Valbenazine:
Tardive dyskinesia—KINECT-3 was a double-blind, placebo-controlled study of 225 patients with tardive dyskinesia. The AIMS score improved by –3.2 for the 80 mg/day group, compared to –0.1 for the placebo group (p <0.001). The number of psychiatric treatment-related adverse events were similar between the active and placebo groups.

Huntington's disease-associated chorea—KINECT-HD was a randomized, double-blind, placebo-controlled trial of 127 patients with Huntington's disease. The total chorea score was improved by –4.6 points for valbenazine compared to –1.4 points for placebo (p <0.001). Valbenazine was not associated with more suicidal ideation or behaviour than placebo.

Dosing and monitoring

Dosing

Deutetrabenazine: Start treatment at 6 mg BD. Increase by 6 mg/day every week, as required, up to a maximum of 24 mg twice daily.

Tetrabenazine: Start treatment at 12.5 mg daily and increase by 12.5 mg every 3–4 days to 12.5 mg bd, then tds. This can then be increased every 4 days, as required/tolerated. The usual maintenance dose is <100 mg/day. The maximum recommended daily dose is 200 mg/day.

Valbenazine: Start treatment at 40 mg once daily. Increase to the recommended dose, 80 mg, at 1 week.

Table 23.61 Pharmacokinetics of α2-adrenergic agonists

	Deutetrabenazine	Tetrabenazine	Valbenazine
Main routes of administration	oral	oral	oral
Bioavailability	80%	>75%	50%
T_{max}	3–4 h	60–90 min	4–8 h
Protein binding	82–85%	82–85%	99%
Metabolism	Hepatic, mainly CYP2D6	Hepatic, mainly CYP2D6	Hepatic, mainly CYP3A4/5
Pharmacologically active metabolites	Yes, strong	Yes, strong	Yes, strong
Elimination half-life	12–16 h	17 h	15–22 h
Excretion	Urine	Urine	60% urine, 30% faeces

Table 23.62 Interactions of VMAT2 inhibitors

Medications which alter VMAT2 inhibitor plasma levels	Pharmacodynamic interactions
All VMAT2 inhibitors: Levels decreased: CYP2D6 inducers, e.g. rifampicin. Levels increased: CYP2D6 inhibitors, e.g. SSRIs such as paroxetine. Valbenazine: Levels decreased: CYP3A4 inducers, e.g. rifampicin, carbamazepine. Levels increased: CYP3A4 inhibitors, e.g. itracanazole	With CNS depressants: can cause increased sedation. With drugs that prolong QTc: may increase the risk of arrhythmia. With antipsychotics, amantadine, and metoclopramide: increased risk of extrapyramidal side effects With MAOi: Risk of hypertensive crisis and serotonin syndrome.

Monitoring

Monitor for depression, suicidality, and parkinsonism.

Pharmacokinetics and interactions

Pharmacokinetics See Table 23.61.
Interactions See Table 23.62.

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Z-Drugs/Nonbenzodiazepine hypnotics

The Z-drugs or nonbenzodiazepine hypnotics are a group of hypnotic benzodiazepine-like drugs that were first marketed in the 1980s. They share a similar mechanism of action and side effect profile to benzodiazepines. They were initially marketed as benzodiazepine alternatives with what was thought to be lower risks of dependence and tolerance. However, this has not been borne out in clinical trials. Physical and psychological dependence can occur with the therapeutic use of any of the Z-drugs. As a result, courses should be kept to a minimum duration, ideally less than 2 weeks including taper. Meta-analyses and reviews conducted so far have suggested that there is little additional benefit from the use of Z-drugs compared to short-acting benzodiazepines such as temazepam, although well-controlled comparative studies are rare.

There is a significant difference in the half-lives of different Z-drugs; Zaleplon and unmodified zolpidem have very short half-lives making them useful in sleep initiation insomnia. Zaleplon can also be used in patients with early awakening as it can be taken closer towards waking than other drugs with minimal effects on next day cognitive ability. In contrast, modified release zolpidem and zopiclone have longer half-lives. This makes them useful agents in the management of patients with sleep maintenance insomnia.

Eszopiclone and Zopiclone

Zopiclone is a racemic mixture of 2 stereoisomers, only one of which is pharmacologically active. It was initially classified as a schedule IV controlled substance in the USA due to its addictive properties and hence not licensed for therapeutic use. In 2005, the isolated active stereoisomer: termed eszopiclone was licensed in the USA—little is known about the clinical differences, other than dosing, between the two drugs. In light of their pharmacological similarities they are believed to be alike in most respects.

Uses

Licensed uses

In the UK

Insomnia:

1. Zaleplon and zolpidem are licensed for the management of insomnia associated with difficulty falling asleep where this disorder is severe enough to be disabling or cause the individual extreme distress, in individuals aged >18 years old.
2. Zopiclone is licensed for the short-term treatment of insomnia, including difficulties getting to sleep, maintaining sleep, and waking early in situations where insomnia is debilitating or causes severe distress, in individuals aged >18 years old.

In the USA

1. Eszopiclone is licensed for the treatment of insomnia in individuals aged >18 years old.
2. Zaleplon: is licensed for the short-term treatment of insomnia in individuals aged >18 years old.
3. Zolpidem (license varies depending on formulation—all for adults >18 years old): Ambien®: short-term treatment of insomnia where there is difficulty of sleep initiation. Ambien CR®: short-term treatment of insomnia where there is difficulty of sleep onset or sleep maintenance. Intermezzo® (sublingual): short-term treatment of insomnia where middle-of-the night wakening is associated with difficulty returning to sleep, provided there are 4 h of bedtime remaining.

Off-label uses

1. RBD (zopiclone used in case studies)
2. Dystonia (zolpidem used in case studies)

Mechanism of action

As with benzodiazepines, the Z-drugs bind with high specificity to GABA-A ligand-gated chloride channel complexes. They potentiate the action of GABA, increasing chloride conductance. The Z-drugs are thought to bind specifically to the $\alpha 1$ subunit whilst benzodiazepine drugs are less subunit selective. This is believed to account for their reduced anticonvulsant and anxiolytic activity compared to certain benzodiazepines.

Toxicity and side effects

- *Common—Neurological*: anterograde amnesia, fatigue, headache, and paraesthesiae. *Genitourinary*: dysmenorrhoea reported with zaleplon.
- *Serious—Dermatological*: angio-oedema has been reported. *Psychiatric*: paradoxical reactions, ranging from mood disorders and nightmare to psychosis.

Contraindications

Absolute: Hypersensitivity to the Z-drug or its excipients, MG, sleep apnoea syndrome, severe respiratory and hepatic impairment. Discontinue Z-drug if the patient develops complex sleep behaviours (e.g. sleep-walking, sleep-driving, and engaging in other activities while not fully awake). Zaleplon is also contraindicated in severe renal impairment.

Relative: Patients with a history of alcohol or substance abuse, chronic respiratory disease, and depression.

In mild-to-moderate hepatic impairment, the maximum dose should be 5 mg for zaleplon and zolpidem and 3.75 mg for zopiclone. In mild-to-moderate renal impairment patients should be monitored closely and lower doses used initially, as clearance may be reduced.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and are also more prone to adverse psychiatric ‘paradoxical’ reactions, e.g. agitation, confusion, and psychosis. They benefit from lower dosing regimens (Eszopiclone: starting dose of 1 mg; usual maintenance dose of 1–2 mg if difficulty getting to sleep is the primary problem. If difficulty staying asleep is the main problem, then 2 mg can be used from the outset. Zaleplon: maximum dose is 5 mg. Zolpidem: maximum dose is 6.25 mg with extended-release tablet, 5 mg standard tablet and 1.75 mg with the sublingual tablet. Zopiclone: the maximum dose is 3.75 mg).
- *Pregnancy*: There are no controlled studies in humans. Animal studies suggest that eszopiclone results in increased rates of post-implantation loss and reduced birthweight, although this hasn’t been demonstrated with other drugs of this class. The manufacturers advise against use in pregnancy. If they are used in pregnant mothers near term, then neonates should be monitored for side effects, including hypothermia, hypotonia, respiratory depression, and sedation.

- *Lactation*: Z-drugs are excreted into breast milk. Manufacturers advise against use due to a lack of data. However, a novel scoring system of psychotropic drugs identified zopiclone as possible to use during breastfeeding. Zaleplon and zolpidem were regarded as not recommended for use.

Efficacy

Zaleplon: As a result of its short duration of action is most effective at reducing sleep latency, with variable impact on total sleep duration. A randomized, double-blind study published in 1999 compared zaleplon with a placebo. Sleep latency was reduced by 15–20 min vs. placebo. Studies looking at memory, learning and psychomotor ability in healthy subjects administered zaleplon, zolpidem, triazolam or placebo at bedtime demonstrated that 10 mg of zaleplon did not impair these abilities at 1.25 h post-dose, whilst zolpidem and triazolam did impair these abilities at this time point.

Zolpidem: A randomized placebo-controlled trial of standard tablet zolpidem used for 35 nights at therapeutic doses demonstrated that zolpidem at 10 mg resulted in a statistically significant improvement in sleep latency but had no significant impact on sleep maintenance. The modified release version of zolpidem has been shown in a further randomized, placebo-controlled trial to have the additional impact of significantly improving sleep maintenance when compared to placebo. Studies differ as to whether psychometric tests performed the day after treatment show impairment, it is likely subtle and more prominent in the elderly.

Zopiclone/Eszopiclone: A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of primary insomnia demonstrated that patients treated with high-dose eszopiclone (3 mg) reported improved sleep and daytime function compared to placebo ($p < 0.001$). Insomnia severity index scores were reduced below clinically significant levels in 50% of patients treated with eszopiclone vs. 19% with placebo ($p < 0.05$). Randomized controlled studies have compared zopiclone with benzodiazepine hypnotics including nitrazepam although none have compared it with the most used dose of temazepam at 10 mg, hence it is difficult to establish superiority between the benzodiazepines and Z-drugs for this indication. Night-time dosing of both eszopiclone and zopiclone is associated with impaired performance in healthy adults the next morning in several psychometric tests. With regards to the older adult, where the impacts of zopiclone on cognitive impairment and psychomotor performance whilst on treatment are more pronounced cognitive behavioural therapy (CBT) has been demonstrated to provide better short- and long-term outcomes when compared to zopiclone. Sleep efficiency improved from 81.4 to 90.1% with CBT compared to a decrease from 82.3 to 81.9% with zopiclone as demonstrated in polysomnographic studies.

Evidence for the use of zopiclone in the treatment of RBD is based on case study evidence; one case series demonstrated that 8 out of 11 patients with RBD found zopiclone effective in managing RBD symptoms. Compared to clonazepam the case series suggested there were less adverse events and episodes of treatment discontinuation because of side effects, which they attributed to the shorter half-life of zopiclone compared to clonazepam.

Dosing and monitoring

Dosing

Zaleplon: Treatment is 10 mg once at night. This should be for as short a period as possible and certainly for no longer than 2 weeks.

Zolpidem: Extended-release tablet: Treatment is 12.5 mg once at night. Standard tablet: Treatment is 10 mg once at night. Sublingual tablet: Treatment is 1.75 mg for women and 3.5 mg for men once at night. Treatment should be for as short a period as possible, usually between 3–14 days, and not exceeding 4 weeks including taper.

Zopiclone/Eszopiclone: Zopiclone: Usual dose is 7.5 mg prior to bed (dosing regimen is the same in insomnia and RBD). Eszopiclone: Start treatment at 2 mg prior to sleep, increase to 3 mg if required. Treatment duration should not be longer than 4 weeks. For management of transient insomnia 2–5 days should be sufficient, short-term insomnia 2–3 weeks.

Monitoring

Patients should be monitored for confusion, particularly the elderly and those with hepatic impairment.

Table 23.63 Pharmacokinetics of Z-drugs

	Eszopiclone	Zaleplon	Zolpidem (unmodified)	Zopiclone
Bioavailability	Not available	~30%	70%	>75%
Tmax	~1 h	~1 h	0.5–3 h	1.5–2 h
Protein Binding	~55%	~60%	~92.5%	~45%
Metabolism	Hepatic: CYP3A4, CYP2E1, and CYP2C8	Hepatic: Aldehyde oxidase > CYP3A4	Hepatic: CYP3A4, lesser degree CYP1A2	Hepatic: CYP3A4, CYP2E1, and CYP2C8
Pharmacologically active metabolites	Yes, weak	No	No	Yes, weak
Elimination half-life	~6 h	~1 h	2.4 h	~5 h
Excretion mechanism	~75% urinary (<10% as unchanged drug)	71% urine (<1% as unchanged drug)	56% urinary and 37% faeces as metabolites	~75% urinary (<10% as unchanged drug)

Table 23.64 Interactions of Z-drugs

Medications which alter Z-drug plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 inducers, e.g. carbamazepine and phenobarbital. **Levels increased:** CYP3A4 inhibitors, e.g. cimetidine, erythromycin. Zaleplon only: Aldehyde oxidase inhibitors, e.g. ondansetron, raloxifene, and TCAs.	**With CNS depressants, e.g. alcohol, anaesthetics, antihistamines, antipsychotics, opioids, and TCAs:** Increased sedative side effects.

Pharmacokinetics and interactions

Pharmacokinetics: See Table 23.63.
Interactions: See Table 23.64.

Food co-ingestion reduces the oral bioavailability of zaleplon and zolpidem. Food also delays Tmax for eszopiclone and zolpidem but has no identified effect on zopiclone pharmacokinetics.

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Chapter 24

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3,4-diaminopyridine (amifampridine)

3,4-DAP was first used in clinical practice in the 1980s and is now the mainstay of symptomatic treatment for Lambert–Eaton myasthenic syndrome (LEMS). Unlicensed preparations were widely used, before amifampridine phosphate (Firdapse®) was licensed in Europe in 2010. They differ from Firdapse® only by minor alterations in chemical structure and are still used in many regions where the cost of Firdapse® is considered prohibitive. Rizurgi® is less stable and therefore requires refrigeration.

Uses

Licensed uses

In the UK/USA

- *LEMS*: Firdapse® is licensed for symptomatic treatment in individuals aged 18 years and older.

Off-label uses

- Congenital myasthenic syndrome and downbeat nystagmus (DBN).

Presentation

- *Trade name*: Firdapse®, Ruzurgi® (licensed only for paediatric patients aged 6–17). Generic amifampridine is not widely available.
- *Formulation*: oral scored tablets, 10 mg.

Mechanism of action

3,4-DAP prolongs presynaptic cell membrane depolarization by blockade of presynaptic voltage-gated potassium channels. This increases the influx of calcium into nerve endings and facilitates exocytosis of acetylcholine-containing vesicles. This action overcomes the effect of VGCC blockade in LEMS, resulting in successful neuromuscular transmission. In DBN, the same mechanism is believed to result in increased excitability of the Purkinje cells of the cerebellum, which may restore their inhibitory function on deep cerebellar and vestibular nuclei.

Toxicity and side effects

- *Common—Cardiovascular*: arrhythmias, palpitations. *Gastrointestinal*: non-specific GI upset. *Neurological*: anxiety, blurred vision, chorea, dizziness, drowsiness, fatigue, headache, myoclonia, oral paraesthesiae, sleep disorders, weakness. *Respiratory*: exacerbation of asthma.

Contraindications

- *Absolute*: epilepsy (3,4-DAP lowers seizure threshold), uncontrolled asthma, and congenital long QT syndromes.
- *Relative*: in renal and hepatic impairment, the manufacturer recommends a smaller starting dose of 5–10 mg and gradual up-titration.

Use in special populations

- *Elderly*: no separate data on safety and efficacy in this group, but this group has an age-related decline in renal and hepatic function, and reduced doses may be required.
- *Pregnancy/lactation*: no safety data. The manufacturer advises avoidance and effective contraception for men and women during treatment with 3,4-DAP.

Efficacy

- *DBN*: a prospective, placebo-controlled study evaluated the effect of a single dose of 3,4-DAP (20 mg) on DBN (*n* = 17, of various aetiologies). Mean peak slow-phase velocity was reduced from 7.2 (SD: 4.2) degrees/s before treatment to 3.1 (SD: 2.5) degrees/s 30 min after treatment ($p < 0.001$). Subjects reported less oscillopsia and felt more stable, while standing and walking. Recently, 3,4-DAP (10 mg) and 4-AP (10 mg) were compared in a double-blind, prospective cross-over study (*n* = 8) for the treatment of DBN. 4-AP was shown to be more effective at 45 and 90 min, as shown by significant reductions in slow-phase velocity.
- *LEMS*: two double-blind, randomized, placebo-controlled discontinuation/withdrawal trials of 3,4-DAP have been undertaken which demonstrated efficacy in LEMS. In the first trial patients (n = 38) were maintained on 15–80 mg in 3 to 4 divided doses of 3,4-DAP for 7–91 days. After which patients (n = 22) were randomized to taper-to-placebo over 14 days or maintained on 3,4-DAP. Efficacy was measured using change from baseline to the end of the discontinuation period in the Quantitative Myasthenia Gravis (QMG) score (physician rated) and in the Subject Global Impression (SGI) (patient rated) score. Change in baseline QMG score and SGI score between the two groups suggested a symptom deterioration in the placebo group QMG: –1.7 (95% CI –3.4–0.0, p = 0.045) and SGI: 1.8 (95% CI 0.7, 3.0, p = 0.003). The second trial randomized patients (n = 26, 1:1) on stable 3,4-DAP to continue the drug or change to placebo for 4 days. Patients who stopped taking the medication noted significant worsening in QMG and SGI scores –6.54 (95% CI –9.78, –3.29, p = 0.0004) and 2.95 (95% CI 1.53, 4.38, p = 0.0003) compared to placebo.

Dosing and monitoring

Dosing

- *DBN*: An observed test dose is often given first. Patients are given either the medication or a placebo, and then the degree of nystagmus, gait, and dynamic visual acuity are assessed pre- and post-dosing. If the test dose is successful, then treatment can be started at 10 mg od, and increased by 10 mg every 1–2 weeks, as required/tolerated, up to 20 mg tds.
- *LEMS*: 15 mg od; 5 mg increments every 4–5 days, up to a maximum of 60 mg/day in 3–4 divided doses.

Monitoring

Perform an ECG at baseline. Commonly, the first test dose is given, while the patient is attached to a cardiac monitor, to assess for the presence of arrhythmia.

Pharmacokinetics and interactions

Pharmacokinetics

Well-absorbed orally, with a bioavailability of 93–100%. Peak plasma concentration by 0.6–1.3 h. Absorption is affected by food, with a 2-fold increase in T_{max}. Time to steady state has not been described in the manufacturer's literature. Metabolized to an inactive 3-*N*-acetylated metabolite. Half-life is around 2.5 h. Amifampridine is fully renally excreted within 24 h, 19% as the parent molecule and 81% as the metabolite.

Interactions

See Table 24.1.

Table 24.1 Interactions of 3,4-DAP (amifampridine)

Pharmacodynamic interactions
With medications which prolong the QT interval, e.g. sultopride: risk of ventricular arrhythmias
With medications which reduce seizure threshold: increased risk of seizures

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Abciximab

Abciximab is a highly potent antiplatelet agent that is licensed as an adjunct to percutaneous coronary intervention. Given its efficacy at preventing antiplatelet aggregation and rapid time to onset it is also used off-licence during neurovascular procedures. It has been available in both Europe and the USA since the mid-1990s.

Uses

Licensed uses

- There are no licensed neurological uses.

Off-label uses

- Abciximab is used during neurovascular interventions suck as angioplasty with or without stent placement and mechanical thrombectomy. It is administered by intra-arterial or intravenous infusion.

Presentation

- *Trade names*: ReoPro®. Generics are not available.
- *Formulations*: Abciximab is available as a 5 mL vial containing 10 mg (2 mg/mL).

Mechanism of action

Abciximab is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3 and binds to the GPIIb/IIIa receptor of human platelets, in order to inhibit platelet aggregation, mainly by preventing the binding of fibrinogen. It also binds to and inhibits the vitronectin ($\alpha_v\beta_3$) receptor (demonstrates procoagulant properties), which is found on platelets, endothelial, and smooth muscle cells.

Toxicity and side effects

- *Common— Haematological:* Bleeding and thrombocytopaenia. *Immunological:* Allergy.
- *Serious—Haematological:* Uncontrollable bleeding and death. *Immunological:* Anaphylaxis.

Contraindications

- *Absolute*: Hypersensitivity to abciximab or its excipients. Active internal bleeding, recent (within 6 weeks) clinically significant gastrointestinal/ genitourinary bleeding, history of cerebrovascular accident (CVA) within two years or CVA at any time with significant neurologic deficit, major surgery/trauma (within 6 weeks), bleeding diathesis, administration of oral anticoagulants (within 7 days) and INR≤1.2, thrombocytopenia (<100cells/μL), severe uncontrolled hypertension, presumed or documented history of vasculitis and use of intravenous dextran before PCI, or intent to use it during an intervention.
- *Relative*: There are no specific dose considerations in hepatic or renal impairment.

Use in special populations

- *Elderly*: No dose adjustment is routinely recommended, although there is little data from use in individuals aged 75 and older. Use with caution, as the elderly are more prone to bleeding.
- *Pregnancy*: No data is available from animal or human studies. Only use in pregnancy if benefits outweigh the risk of potential harm to the fetus.
- *Lactation*: There is no data from animal or human studies. Abciximab is a large molecule and hence it is both unlikely to be present in significant

quantities in breastmilk and unlikely to be absorbed from the infants gastrointestinal tract. Given the lack of available data it should only be used if the potential benefits outweigh the risks. If it is used whilst breastfeeding, the infant should be monitored for any signs of bleeding.

Efficacy

There are no randomized controlled trials that have evaluated the role of abciximab in neurointerventional procedures. There have been four phase III clinical trials, which have demonstrated the additional benefit of adding abciximab in percutaneous coronary intervention for the management of myocardial infarction. There have been several case series and one case-control study that have described the investigators experience of using abciximab during neurovascular interventions:

The largest identified cohort involved 42 patients who were treated with abciximab following intraprocedural thromboembolic complications of aneurysm coil embolization. Abciximab was administered (Intra-arterial (IA) or IV) as a rescue therapy, in adjunct to intraprocedural heparin and aspirin as well as pre-procedural clopidogrel. No haemorrhagic complications were observed. Intracarotid abciximab administration has also been tried as a rescue therapy for middle cerebral artery occlusion during carotid angioplasty (n = 3), with complete resolution of symptoms and without any reported mortality or adverse effects. In a case-control study, IV abciximab was compared to heparin in patients undergoing carotid angioplasty. There was a non-significant trend towards less risk of ischaemic complications in the abciximab compared to the heparin group (1/37 vs. 4/33). The incidence of minor or major haemorrhagic complications were comparable between these groups (5%).

Dosing and monitoring

Dosing

Patients should receive a bolus loading dose of 0.25 mg/kg, followed by 10 μg/min IV infusion (or a weight-adjusted rate of 0.125 μg/kg/min, up to a maximum of 10 μg/min).

Monitoring

Patients should be monitored for bleeding complications. Platelet transfusion can restore (at least in part) platelet function in the event of severe bleeding complications.

Pharmacokinetics and interactions

Pharmacokinetics

Steady state can be achieved promptly after starting infusion, with constant free plasma abciximab concentration throughout the infusion.

- If only a bolus dose is administered: Rapid, dose-dependent platelet function inhibition is noted, after which the free plasma concentration decreases rapidly (initial half-life of less than 10 min), and the platelet-bound concentration decreases at a slower rate (second half-life of 30 min). At 2 h post-injection (bolus of 0.25–0.3 mg/kg), over 80% of the GPIIb/IIIa receptors were blocked without any platelet aggregation in response to 20 μM ADP administration.

- After infusion ceases: Free plasma concentrations fall rapidly for the first 6 h, and then decline follows a slower rate; platelet function recovers over the next 48 h; abciximab remains in a platelet-bound form for 15 days with some persistent, low-level blockade. The bleeding time returns to ≤12 min within 12 h in 75% and within 24 h in 90% of patients following infusion cessation.

Interactions

Formal drug interaction studies with abciximab have not been conducted. Heparin, other anticoagulants, thrombolytics, and antiplatelet agents are associated with an increased risk of bleeding.

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Acetazolamide

Acetazolamide can be used as a broad-spectrum anti-seizure medication (ASM) (predominantly as an adjunct) and is also commonly used in the management of idiopathic intracranial hypertension. It benefits from a rapid onset of action and few pharmacological interactions. Its usefulness in epilepsy is limited by tolerance which can develop within 1–6 months of initiating therapy.

Uses

Licensed uses

In the UK/ USA

- *Epilepsy*: acetazolamide is licensed for treatment as an adjunct of atonic, atypical absence, myoclonic, tonic, and generalized tonic–clonic seizures in individuals of all ages.

Off-label uses

- Catamenial seizures, episodic ataxias, continuous spike and wave in slow-wave sleep, Landau–Kleffner syndrome, Lennox–Gastaut syndrome, idiopathic intracranial hypertension, and periodic paralyses.

Presentation

- *Trade names*: Diamox® and Diamox® SR. Generics are available.
- *Formulations*: Diamox® is available as a modified-release capsule, a powder for reconstitution, IM or IV injection (as a sodium salt), and as a tablet. Modified-release capsule: 250 mg. Powder for reconstitution: 500 mg per vial. Tablet: 250 mg.

Mechanism of action

- *Epilepsy*: acetazolamide is a carbonic anhydrase inhibitor. The exact mechanism of action in epilepsy is unclear. Its action may be mediated by inhibition of cerebral carbonic anhydrase enzymes or by systemic lowering of the pH, resulting in lowering of intracellular pH and suppression of neuronal activity. When used as an adjunct, a proportion of its effect may be due to increased tissue absorption of other AEDs such as phenytoin and phenobarbital.
- *Idiopathic intracranial hypertension*: acetazolamide is believed to reduce the formation of CSF by inhibiting the action of choroid plexus carbonic anhydrase activity.

Toxicity and side effects

Carbonic anhydrase inhibitors reduce intracellular pH, resulting in an increased incidence of hypokalaemia, metabolic acidosis, nephrolithiasis, paraesthesiae, polydipsia, and polyuria.

- *Common—Dermatological*: allergic rash. *Endocrine*: reduced libido. *Gastrointestinal*: anorexia, diarrhoea, nausea, and parageusia. *Neurological*: dizziness, headache, and paraesthesiae.
- *Serious—Dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Haematological*: rarely blood dyscrasias and bone marrow suppression.

Contraindications

- *Absolute*: pre-existing adrenocortical insufficiency due to its tendency for potassium loss, cirrhosis due to its predisposition for hyperammonaemia, pre-existing metabolic acidosis, and severe renal impairment. In addition, it should be avoided in patients treated with high-dose aspirin, as the combination has been reported to result in tachypnoea, loss of appetite, coma, and even death.
- *Relative*: the dose should be lowered in mild to moderate renal impairment (eGFR <60 mL/min/1.73 m^2). It should be used with caution in patients with hyponatraemia, hypokalaemia, a history of sulfonamide-induced allergic rash, and those with a previous history of nephrolithiasis or on treatments predisposing to stone formation, including topiramate and zonisamide. It should not be given to patients who are undergoing sustained treatment for chronic angle-closure glaucoma.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic interactions is high.
- *Pregnancy*: some animal studies have demonstrated teratogenic effects; however, there are no controlled studies in humans. Use in pregnancy involves weighing up the potential benefits and side effects. Most would use alternative means of controlling CSF pressure in IIH, including weight control, regular lumbar puncture, or a neurosurgical procedure.

The pharmacokinetics of acetazolamide during pregnancy have not been adequately studied.

- *Lactation*: acetazolamide is present in breast milk. Infant's plasma levels are 4–9% of maternal plasma levels, and this is thought to be too low to be harmful. If used, infants should be monitored for potential side effects. They should be switched to alternative methods of feeding if these are identified.

Efficacy

- *Epilepsy*: there is little good-quality evidence available as to the clinical efficacy of acetazolamide in epilepsy. What evidence there is comes from the 1950s and suggests that acetazolamide is a broad-spectrum ASM, prone to the development of tolerance after 1–6 months. The tolerance is eliminated by intermittent use, making it useful if an ASM is needed for short periods, e.g. catamenial epilepsy.
- *Idiopathic intracranial hypertension*: For discussion of the evidence base for use in IIH, please see the IIH section, pp. 14–15.

Dosing and monitoring

Dosing

- *Epilepsy*: the PO and IV dosages are between 0.25 g and 1 g daily in divided doses.
- *Idiopathic intracranial hypertension*: acetazolamide can be started at 250–500 mg bd for IIH (or 15–25 mg/kg/day in 2–3 divided doses), and increased according to response. Suggested dose increments are 15–25 mg/kg at weekly intervals. Doses of up to 2–4 g/day may be used. Side effects are dose-related, and higher doses may not be tolerated by some patients.

Monitoring

Not recommended routinely. Serum bicarbonate can be monitored, if necessary.

Pharmacokinetics and interactions

Pharmacokinetics

Acetazolamide has good oral absorption, with bioavailability >90%. It reaches maximum plasma concentrations (T_{max}) at 2–4 h, and steady state in 2 days. It does not undergo hepatic metabolism. Hundred per cent of the dose is ultimately excreted unchanged by the kidneys. The half-life is 10–15 h.

Interactions

See Table 24.2.

Table 24.2 Interactions of acetazolamide

Medications whose plasma levels are altered by acetazolamide	Pharmacodynamic interactions
Levels increased: carbamazepine, ciclosporin, phenobarbital, and phenytoin.	With other carbonic anhydrase inhibitors and bicarbonate: increased risk of nephrolithiasis
Levels decreased: lithium and primidone	With high-dose aspirin: risk of tachypnoea, anorexia, sedation, and even death

References

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Aciclovir

Aciclovir has been used in the management of herpes virus infections since the 1980s. It is most effective against HSV 1 and 2, to a lesser extent herpes zoster (VZV), and has only minimal effectiveness against CMV and EBV. It needs to be started without delay if herpes encephalitis is suspected, and continued for at least 2–3 weeks, potentially longer in the immunosuppressed.

Uses

Licensed uses

In the UK/USA

- *Aciclovir is licensed for the treatment of herpes simplex and varicella zoster infections, in individuals of all ages.*

Off-label uses

- None.

Presentation

- *Trade names*: Zovirax®. Generics are available.
- *Formulations*: aciclovir is available in multiple enteral and parenteral formulations. For the purposes of herpes encephalitis, only the IV form should be used. This is available as a powder for reconstitution and IV infusion and as a sterile concentrate. *Powder for reconstitution and IV*

infusion: 250 mg. *Sterile concentrate*: 10 mL, 20 mL, and 40 mL at 25 mg/mL. For less severe infections aciclovir is available as an oral suspension and tablet. *Oral suspension*: 200 mg/5 mL. *Tablet*: 200 mg, 400 mg, and 800 mg.

Mechanism of action

Aciclovir is a purine nucleoside analogue. It specifically interacts with the viral thymidine kinase enzyme, leading to the creation of aciclovir triphosphate, a false substrate for viral DNA polymerase which, when incorporated into a new DNA chain, results in termination, thereby preventing DNA replication.

Toxicity and side effects

- *Common—dermatological*: allergic rash, phlebitis with IV infusion, photosensitivity, pruritus, and urticaria. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, reversible changes in hepatic enzymes, and vomiting. *Neurological*: fatigue and headache. *Renal*: impaired renal function.
- *Serious—dermatological*: severe local inflammatory reactions, potentially resulting in necrosis, may occur with tissue extravasation during IV infusion. Anaphylaxis and angio-oedema are rare. *Gastroenterological*: hepatitis. *Haematological*: anaemia, leucopenia, and thrombocytopenia have been reported. *Neurological*: severe neurological reactions, including ataxia, convulsions, tremors, and even coma can occur. *Psychiatric*: psychosis can occur. *Renal*: acute kidney injury, particularly with IV infusions—this can be minimized by slow IV infusions and ensuring adequate hydration.

Contraindications

- *Absolute*: hypersensitivity to aciclovir, its excipients, or valaciclovir.
- *Relative*: use with caution in patients with underlying neurological abnormalities or previous neurological reactions to cytotoxic drugs, or who are co-prescribed IFN or intrathecal methotrexate, as these groups may be more prone to neurological side effects.

In renal impairment, the dose will need to be reduced.

- For the IV formulation: if CrCl is 25–50 mL/min, give 5–10 mg/kg bd, rather than tds; if CrCl is 10–25 mL/min, give 5–10 mg/kg od. If the patient has haemodialysis or peritoneal dialysis, i.e. CrCl 0–10 mL/min the dose 5–10 mg/kg should be halved and given once daily after dialysis.
- For the oral formulation: if the eGFR is <10 mL/min/1.73 m^2, use the 800 mg bd for herpes zoster infections; if the eGFR is 10–25 mL/min/1.73 m^2, use 800 mg tds.

No dose adjustments are required in hepatic impairment, although it should be used with caution in severe impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens. The elderly are also more likely to get neuropsychiatric side effects and worsening renal function; hence urea and electrolytes (U&Es) should be frequently monitored.

- *Pregnancy*: limited data are available regarding the use of aciclovir in pregnancy. Small registries of human births and animal studies have not shown teratogenicity. However, aciclovir does cross the placenta, so the manufacturers advise against use, unless the benefits outweigh the risks.
- *Lactation*: aciclovir is present in breast milk. Even when taken at the highest maternal dosage breastmilk contains about 1% of average infant dosing. No adverse events have yet to be reported with infant consumption through breast milk. Caution is advised with its use while breastfeeding.

Efficacy

Compared to historic controls before the use of effective antivirals, aciclovir cuts the mortality rate from herpes simplex encephalitis by approximately two-thirds (from 70% to 20% case-based mortality). Increasing duration of symptoms prior to initiation of treatment is strongly associated with poorer outcome. Early treatment is defined by being (1) before the loss of consciousness, (2) within 24 h of the onset of symptoms or when a patient's GCS is between 9 and 15. For herpes zoster encephalitis, aciclovir is used based on case study evidence and expert consensus; there are no controlled studies.

Dosing and monitoring

Dosing

Herpes encephalitis: administer 10 mg/kg IV tds for a minimum of 14–21 days for herpes simplex, and 14 days for herpes zoster. The need for ongoing treatment should be guided by the presence or absence of positive viral CSF PCR results, following a standard treatment course, and clinical response. Immunocompromised patients need longer courses.

Ramsay **Hunt Syndrome/Bell's Palsy associated with VZV infection):** 400 mg orally 5 times daily for 10–14 days in combination with corticosteroids (e.g. 40–60 mg of prednisolone for 10–14 days, including taper); begin within 3 days of symptom onset. Intravenous aciclovir can be considered for severely unwell patients as per encephalitis doses.

Monitoring

Renal function, FBC, and liver function should be monitored frequently during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

The terminal plasma half-life of aciclovir after IV infusion is ~3 h; this can be prolonged to 20 h in chronic renal failure. CSF levels reach 50% of corresponding plasma levels. Protein binding is 10–30%. Aciclovir is mainly eliminated via the renal tract, 75–80% as unchanged drug and 10–15% as the major metabolite 9-carboxymethoxymethylguanine.

Interactions

See Table 24.3.

Table 24.3 Interactions of aciclovir

Medications whose plasma levels are altered by aciclovir	Medications whose plasma levels are altered by aciclovir	Pharmacodynamic interactions
Levels increased: cimetidine, mycophenolate mofetil (metabolite), probenecid, tenofovir, and theophylline	Levels increased: mycophenolate mofetil (metabolite)	With nephrotoxics: increased risk of acute kidney injury With herpes zoster vaccine: may diminish the effect of the vaccine

References

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Ellul M, Solomon T. Acute encephalitis—diagnosis and management. *Clin Med (Lond)* 2018;18(2):155–9.

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Alemtuzumab

This drug, initially marketed as Campath®, was developed to treat B-cell chronic lymphocytic leukaemia. It was licensed for the treatment of relapsing-remitting multiple sclerosis (RRMS) in the UK in 2014.

Uses

Licensed uses

In the UK/USA

- *MS*: In the UK, alemtuzumab is licensed for the treatment of RRMS in individuals with highly active disease in spite of a full course of one disease-modifying therapy (DMT), or patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. In the USA, its use is indicated in RRMS and secondary progressive disease where its use is generally reserved for patients who have had an inadequate response to 2 or more drugs indicated in the treatment of MS.

Off-label uses

- None.

Presentation

- *Trade name*: Lemtrada®. Generics are not available.
- *Formulation*: a concentrate for IV infusion (10 mg/mL): 12 mg.

Mechanism of action

Alemtuzumab is a humanized IgG1-kappa monoclonal antibody specific for CD52 on the cell surface of B and T lymphocytes. It mediates cell lysis by complement fixation and cell-mediated cytotoxicity. This induces a prolonged depletion of circulating lymphocytes. B cells recover rapidly, but T cells can take up to 5 years to return to baseline levels.

Toxicity and side effects

- *Common—endocrine*: thyroid dysfunction. *Psychiatric*: anxiety and insomnia.
- *Serious—cardiovascular*: arrhythmia, cardiac failure, pericarditis, and MI. *Gastrointestinal:* Acalculous cholecystitis. *Haematological*: anaemia, immune thrombocytopenic purpura (ITP), lymphopenia, neutropenia, acquired haemophilia A and Haemophagocytic lymphohistiocytosis (HLH). *Immunological*: ITP, Autoimmune hepatitis, autoimmune nephropathies (anti-GBM), and thyroid dysfunction. Anaphylaxis infusion reactions (dyspnoea, fever, hypotension, rash, tachycardia, and urticaria) and opportunistic infections. *Infection:* Bacterial and viral infections. *Renal*: autoimmune-related kidney disease, including anti-glomerular basement membrane disease. *Respiratory*: acute respiratory distress syndrome. *Neurological*: Haemorrhagic stroke and progressive multifocal leukoencephalopathy (PML). *Vascular:* Dissection of the cervicocephalic arteries.

Contraindications

- *Absolute*: hypersensitivity to alemtuzumab (or murine proteins), active systemic infections, HIV, and active malignancy.
- *Relative*: the effects on patients with renal or hepatic impairment have not been studied, and caution is advised.

Use in special populations

- *Elderly*: alemtuzumab has not been studied in the elderly.
- *Pregnancy*: the teratogenicity of this drug is not known, but it is contraindicated in pregnancy. Active contraception should be used during, and for 6 months after, treatment.
- *Lactation*: breastfeeding should be avoided during and for 4 months following the last infusion.

Efficacy

The *CARE-MS I* trial compared alemtuzumab to 44 mcg SC IFN-β-1a three times a week in patients who had not previously been treated with DMTs. The relapse rate over 2 years was 22% with alemtuzumab, compared to 40% with Interferon Beta-1a ($P<0.0001$). With no significant effect on 6-month disability progression. The *CARE-MS II* trial again compared alemtuzumab to 44 mcg SC IFN-β-1a three times a week. The relapse rate over 2 years was

49% lower, compared to IFN, and the risk of 6-month sustained accumulation of disability was reduced by 42% ($p = 0.0098$).

Over a median 7-year follow-up, most (52%) patients received just two cycles; 36% required three cycles, 8% four, and 1% five. Disease stabilization was seen in the majority of patients, with 67.8% showing improved or unchanged 6-month sustained disability, compared with baseline, and 59.8% showing overall improvement or stabilization of disability using an area under the curve analysis. Secondary autoimmunity was the most frequently observed side effect, occurring in 47.7% patients, commonly involving the thyroid gland.

Dosing and monitoring

Dosing

IV infusion of 12 mg each day for 5 consecutive days, followed by 12 mg each day for 3 days after 1 year.

Monitoring

Patients should be pre-treated with corticosteroids (1 g methylprednisolone for at least the first 3 days of the treatment course), antihistamines, and oral aciclovir (200 mg bd for 1 month) to prevent herpes zoster infections. Patients should be observed for infusion reactions, which can be severe. Prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) is used for a minimum of 2 months and until the CD4 count exceeds 200×10^6/L. There is a significant risk of thrombocytopenia and neutropenia during treatment. FBC should be measured before, and at regular intervals (current recommendation is monthly) during treatment . If platelet counts fall below 25×10^9/L or neutrophil counts fall below 0.25×10^9/L, alemtuzumab should be withheld. The drug should be permanently discontinued if autoimmune thrombocytopenia or anaemia develops. Thyroid function tests (TFTs) and urinalysis should also be monitored regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Clearance decreases with repeated doses, due to the reducing numbers of CD52 receptors in the periphery. With accumulation in the plasma, the rate of elimination reaches zero-order kinetics. The half-life is 8 h following the initial dose and increases up to 6 days after repeated doses.

Interactions

Patients should only ever receive irradiated blood products following treatment, due to the risk of transfusion-associated graft-versus-host disease. Patients should not receive live vaccines for 12 months following treatment.

References

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Tuohy O, Costelloe L, Hill-Cawthorne D, *et al*. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 2015;86(2):208–15.

Amantadine

Amantadine was first marketed in the 1960s for the treatment of influenza. It was serendipitously found to have a beneficial effect on the symptoms of Parkinson's disease (PD) in patients treated for influenza in 1968. It can be used as monotherapy or as an adjunct to levodopa, particularly in those with troublesome levodopa-induced dyskinesias (LID).

Uses

Licensed uses

In the UK/USA

- *PD*: amantadine is licensed for the treatment of PD in individuals aged 10 years and older in the UK, and 1 year and older in the USA.

In the USA

- *Drug-induced extrapyramidal syndrome*: amantadine is also licensed for the treatment of drug-induced extrapyramidal side effects in individuals aged 1 year and older.
- *The extended-release capsules/tablets are available in the USA and not UK*: They are licensed for the treatment of LID in individuals with Parkinson's.

Off-label uses

- Chorea and MS-related fatigue.

Presentation

- *Trade names*: Standard capsule: Lysovir®, Symmetrel®, Extended-release: Osmolex ER®, Gocovri®. Generics of the standard release are available.
- *Formulations*: amantadine is available as a capsule and a syrup. Capsule: 100 mg. Syrup: 50 mg/5 mL in a 150 mL bottle. The extended-release capsule Gocovri® is available as a 68.5 mg and 137 mg capsule. The extended-release tablet Osmolex ER® is available at 129 mg, 193 mg, and 258 mg of amantadine. It consists of an immediate-release outer layer and slow-release core.

Mechanism of action

The exact mechanism of action in the treatment of PD is unknown; proposed mechanisms include: inhibition of dopamine reuptake and enhanced dopamine release at the presynaptic membrane, post-synaptic upregulation of D2 receptors, antimuscarinic activity, and non-competitive NMDA receptor antagonism (NMDA receptor blockade has been shown to reduce the severity of LID in monkey models of PD).

Toxicity and side effects

- *Common—cardiovascular*: orthostatic hypotension and peripheral oedema. *Dermatological*: livedo reticularis. *Gastrointestinal*: anorexia, constipation, diarrhoea, dry mouth, and nausea. *Neurological*: ataxia, dizziness, dream abnormality, fatigue, headache, insomnia, somnolence. *Psychiatric*: agitation, anxiety, confusion, delirium, depression, and hallucinations.
- *Serious—Haematological*: agranulocytosis. *Neurological*: lowered seizure threshold and neuroleptic malignant syndrome (NMS) (related to dosage reduction or sudden withdrawal). *Ophthalmological*: corneal oedema. *Psychiatric*: mania, psychosis, and suicide.

Contraindications

- *Absolute*: known hypersensitivity to amantadine, severe renal impairment (CrCl <15 mL/min).
- *Relative*: use with caution in angle-closure glaucoma, underlying neuropsychiatric disorders, cardiovascular disorders, and known seizure disorder (lowers seizure threshold). No dose alteration in hepatic impairment. In renal impairment, reduce the standard-release dose to 100 mg every 2–3 days if CrCl is 15–35 mL/min.
- For the extended-release capsule Gocovri®: start treatment at 68.5 mg once daily, use a max dose of 137 mg once daily if CrCl 30–59 mL/min; if CrCl is 15–29 mL/min reduce dose of 68.5 mg once daily.
- For the extended-release tablet Osmolex ER®: start treatment at 129 mg and increase every 3 weeks as required if CrCl 30–59 mL/min. Give one dose every 48 h. If CrCl 15–29 mL/min start treatment at 129 mg and increase every 4 weeks. Given one dose every 96 h. Monitor renal function carefully, particularly in patients on the maximum dosage of 322 mg.

Use in special populations

- *Elderly*: the elderly experience an age-related reduction in renal function and are more prone to side effects, including orthostatic hypotension; hence a lower dosing regimen may be appropriate.
- *Pregnancy*: teratogenicity noted in animal studies and case reports in humans; use in pregnancy is contraindicated.
- *Lactation*: amantadine is present in milk; amantadine may reduce serum prolactin (although this may not affect lactation) hence its manufacturers advise avoidance in nursing mothers.

Efficacy

A randomized, placebo-controlled trial of amantadine (300 mg/day) was conducted in advanced-PD patients with motor fluctuations and dyskinesias treated with levodopa. Amantadine treatment was superior to placebo in suppressing dyskinesias, with an average duration of effect of 4.9 vs. 1.3 months with placebo ($p < 0.001$). There was an increase in 'on' time and a decrease in 'off' time; however, neither was significant. Extended-release amantadine has been shown in a randomized, double-blind, placebo-controlled trial to significantly reduce the Unified Dyskinesia Rating Scale by 15.9 vs. 8 for placebo ($p < 0.001$).

Dosing and monitoring

Dosing

Standard release: Start treatment at 100 mg od and increase to 100 mg bd at 1 week. This is the usual maintenance dose, although amantadine can be further uptitrated by 100 mg a week to a maximum dose of 400 mg/day, if required. Onset of effect may be seen after 1–2 days but may be lost after a few months.

Extended-release Gocovri®: Start treatment at 137 mg od at night. Increase to 274 mg once daily at night at one week.

Extended-release Osmolex ER®: Start treatment at 129 mg od in the morning. Increase as required in weekly intervals to a max. dose of 322 mg.

Monitoring

None required.

Pharmacokinetics and interactions

Pharmacokinetics

Standard capsule: Oral bioavailability is 66–100%. T_{max} is 3–4 h. Steady state is reached at 3 days. Sixty-seven per cent is protein-bound (plasma proteins and red blood cells). Amantadine undergoes minimal metabolism by *N*-acetylation. The elimination half-life is 90%; the predominant mechanism is renal secretion, ~90% as unchanged drug.

Extended release: The median T_{max} is 12 h for GOCOVRI™ and 7.5 h for Osmolex ER®. Steady state is reached at 3–4 days. The pharmacokinetics are otherwise the same as the standard capsule.

Interactions

See Table 24.4.

Table 24.4 Interactions of amantadine

Medications which alter amantadine plasma levels	Pharmacodynamic interactions
Levels increased: drugs which impair renal clearance (e.g. thiazide diuretics, and trimethoprim)	With anticholinergics: can enhance the anticholinergic effects of amantadine With CNS depressants, e.g. alcohol: may increase CNS toxicity

References

Fox S, Katzenschlager R, Lim S, *et al*. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2018;33(8):1248–66.

Metman L, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol* 1999;56(11):1383–6.

Pahwa R, Tanner CM, Hauser RA, *et al*. ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study): a randomized clinical trial. *JAMA Neurol* 2017;74(8):941–9.

Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004;75(1):141–3.

Ammonium tetrathiomolybdate

Ammonium tetrathiomolybdate, an unlicensed agent previously used to treat copper toxicosis in animals, is emerging as a potential new chelating treatment in Wilson's disease (WD). Its improved side effect profile, in particular the reduced incidence of neurological deterioration on initiation of treatment (compared to the existing chelating therapies available for WD) and the encouraging results from short-term clinical efficacy studies have promoted this off-label use.

Uses

Licensed uses

In the UK/USA

- Ammonium tetrathiomolybdate has no licensed uses in the USA. It has been given orphan designation for the treatment of WD by the European Medicines Agency.

Off-label uses

- WD.

Presentation

- *Trade names*: None.
- *Formulations*: Oral tablet.

Mechanism of action

Ammonium tetrathiomolybdate acts to reduce total body copper in two ways; firstly, it binds copper from both food and endogenously secreted intestinal copper, to form a complex which prevents intestinal copper absorption. Secondly, when absorbed, tetrathiomolybdate complexes available copper with albumin, thereby preventing cellular absorption and increasing systemic copper removal.

Toxicity and side effects

- *Common—gastrointestinal/hepatic*: a mild elevation of aminotransferase enzymes has been observed in some clinical studies (~5% of patients). This effect occurs much less frequently if the daily dose does not exceed 120 mg and is quickly responsive to a drug holiday and/or dose reduction.
- *Serious—haematological*: the predominant adverse effect observed in clinical studies is mild bone marrow suppression, producing anaemia, leucopenia, and occasionally thrombocytopenia. This is probably because the bone marrow requires copper for cellular proliferation. It is a dose-related effect; it occurs much less frequently if the daily dose does not exceed 120 mg and is quickly responsive to a drug holiday and/or dose reduction. *Neurological*: deterioration of the neurological manifestations of WD occurs in ~4%.

Contraindications

- *Absolute*: hypersensitivity to ammonium tetrathiomolybdate.
- *Relative*: studies have not been performed in patients with hepatic or renal impairment; hence no guidance with regard to dose adjustment can be recommended—use with caution.

Use in special populations

- *Elderly/pregnancy/lactation*: there are no data on the safety and efficacy of tetrathiomolybdate in patients above 65 years of age, those who are pregnant, or nursing mothers; use with caution.

Efficacy

An open-label study of 55 patients presenting with neurological symptoms of WD treated with tetrathiomolybdate showed that the neurological symptoms worsened in only 4% of patients (2 of 55) during the 8 weeks of tetrathiomolybdate treatment, as indicated by serial quantitative neurology and speech scores. Serum copper was lowered to 25% or less than baseline.

When comparing tetrathiomolybdate with trientine, a double-blind RCT of 48 patients with neurological symptoms of WD demonstrated that deterioration of these neurological symptoms occurred in only 4% of patients (1 of 25), compared to 26% in the trientine arm ($p < 0.05$). Furthermore, at a 3-year period, patients initially treated with tetrathiomolybdate recovered an average of 81% of their neurological function (vs. 51% with trientine).

Dosing and monitoring

Dosing

In the RCT by Brewer and colleagues, patients received tetrathiomolybdate in doses of 20 mg tds with meals and 20 mg tds in between meals. This was co-prescribed with 50 mg BD of zinc.

Monitoring

Regular monitoring of FBC, and liver profile should be undertaken.

Pharmacokinetics and interactions

Pharmacokinetics

- Pharmacokinetic studies have not been carried out.

Interactions

- None as yet reported.

References

Brewer GJ, Askari F, Lorincz MT, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Arch Neurol* 2006;63(4):521–7.

Brewer GJ, Hadera P, Kluin KJ, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate: III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003;60(3):379–85.

Hedera P. Update on the clinical management of Wilson's disease. *Appl Clin Genet* 2017;10:9–19.

Andexanet alfa

Andexanet alfa was first approved by the Food and Drug Administration (FDA) in 2018. It is a recombinant FactorXa protein, which acts to rapidly reverse the anticoagulant effect of both apixaban and rivaroxaban.

Uses

Licensed uses

In the UK/USA

- For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Off-label uses

- Reversal of anticoagulation in patients taking edoxaban.

Presentation

Andexanet alfa is formulated as a powder for reconstitution and infusion.

- *Trade names*: Andexxa® and Ondexxya®. Generics are not available.
- *Formulations*: andexanet alfa 200 mg in a vial for reconstitution.

Mechanism of action

Andexanet alfa, is a form of recombinant FXa. It is catalytically inactive due to a substitution of serine for an alanine residue. This means it is unable to activate prothrombin. It binds the FXa inhibitor rendering them inactive and preventing their effect on the coagulation cascade.

Toxicity and side effects

- *Common—Cardiovascular*: palpitations. *Gastrointestinal*: abdominal pain, dry mouth, dysgeusia, and nausea. *Haematological*: elevation of D-dimer and F1 and F2 fragments. *Immunological*: allergic reaction. *Neurological*: tinnitus. *Respiratory*: cough, dyspnoea.
- *Serious—Cardiovascular:* 10.3% of patients in the ANNEXA-4 study experienced VTE, MI, and stroke during the 30-day follow-up period. 27.8% of patients had restarted antithrombotic therapy at the time of the event, and all of the patients had been anticoagulated for a prior history of VTE and/or atrial fibrillation at the time of receiving andexanet alfa.

Contraindications

- *Absolute:* Hypersensitivity reactions to active substance or components of formulation.
- No dose alterations are required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: No dose alteration is required.
- *Pregnancy*: No data is available. The manufacturer advises avoiding use in pregnancy.
- *Lactation*: No data is available. Manufacturers advise discontinuing breastfeeding during treatment.

Efficacy

ANNEXA-A and ANNEXA-R: In ANNEXA-A, subjects received oral apixaban 5 mg twice daily for 3.5 days, and in the ANNEXA-R study, subjects received oral rivaroxaban 20 mg/day for 4 days. Subjects were randomized 3:1 (ANNEXA-A) or 2:1 (ANNEXA-R) to receive coagulation factor Xa (recombinant) or matching placebo. Each study was performed in 2 consecutive parts: Part 1 examined a coagulation factor Xa (recombinant) IV bolus alone, and part 2 examined a coagulation factor Xa (recombinant) IV bolus followed by a continuous 120-min infusion. In ANNEXA-A, participants received coagulation factor Xa (recombinant) as a 400 mg IV bolus (part 1) or as a 400 mg IV bolus followed by a continuous infusion of 4 mg/min for 120 min (part 2). In ANNEXA-R, subjects received coagulation factor Xa (recombinant), inactivated-zhzo as an 800 mg IV bolus (part 1) or as an 800 mg IV bolus followed by a continuous infusion of 8 mg/min for 120 min (part 2).

A bolus dose of andexanet alfa significantly reduced anti-factor Xa activity compared with placebo in both the apixaban study (mean ± SD reduction, 94 ± 2% vs. 21 ± 9%; $p < 0.001$) and the rivaroxaban study (92 ± 11% vs. 18 ± 15%; $p < 0.001$). In Part 2 of the studies, the results also showed a significant reduction in anti-factor Xa activity in the apixaban study (92 ± 3% vs. 33 ± 6%; $p < 0.001$) and the rivaroxaban study (97 ± 2% vs. 45 ± 12%; $p < 0.001$). The effects of andexanet alfa in both parts of the trial lasted for approximately 1–2 h following administration of the bolus dose (trial Part 1) or after completion of the infusion (trial Part 2).

ANNEXA-4 assessed the haematostatic effects of andexanet alfa in patients enrolled with acute major bleeding (n = 479) within 18 h of anti-FXa administration. Major bleeding was predominantly intracranial and gastrointestinal. Excellent or good hemostasis was achieved in 80% (95% CI, 75–84) of evaluable patients (274 of 342).

Dosing and monitoring

Dosing

Administered as either low dose or high dose.

Low-dose regime (Total 5 vials): IV bolus at target rate of 30 mg/min over 15 min followed by continuous infusion of 4 mg/min.

High-dose regime (Total 9 vials): IV bolus at target rate of 30 mg/min over 30 min followed by continuous infusion of 8 mg/min.

Low-dose regime is used for apixaban 5 mg or lower or rivaroxaban 10 mg or lower. If timing from last apixaban or rivaroxaban is 8 h or greater then use low-dose regime regardless of FXa dose. Use high-dose regime if the apixaban dose was greater than 5 mg or unknown or if the rivaroxaban dose was greater than 10 mg or unknown. The dose referred to is the last dose, rather than total over 24 h.

Monitoring

Treatment monitoring should be based mainly on clinical parameters indicative of appropriate response (i.e. achievement of haemostasis), lack of efficacy (i.e. re-bleeding), and adverse events (i.e. thromboembolic events). Treatment monitoring of andexanet alfa should not be based on anti-FXa-activity. Commercial anti-FXa-activity assays are unsuitable for measuring anti-FXa activity following administration of andexanet alfa as these assays result in erroneously elevated anti-FXa activity levels, thereby causing a substantial underestimation of the reversal activity of andexanet alfa.

Pharmacokinetics and interactions

Pharmacokinetics

The half-life appears to be approximately 1 h. Administration of andexanet alfa bolus has resulted in reversal of anti-factor Xa activity for 2 to 4 h. Coagulation factor Xa (recombinant) has been administered as an IV bolus push followed by a 1–2-h infusion to extend the action of the drug.
Interactions No interaction studies with andexanet alfa have been performed.

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Aspirin

Aspirin is a salicylic ester of acetic acid. It has a wide range of clinical uses, owing to its analgesic, antipyretic, anti-inflammatory, and antithrombotic properties. It was first marketed in the UK in 1939.

Uses

Licensed uses

In the UK

- Cerebrovascular disease: aspirin is licensed for the secondary prevention of thrombotic cerebrovascular disease in individuals aged 16 years and older.

In the USA

- Cerebrovascular disease: aspirin is licensed for the prevention and treatment of acute stroke and TIA in individuals aged 12 years and older.

Off-label uses

- Prevention of stroke in patients with AF, treatment of thrombotic complications of neuro-Bechet’s and SLE, and treatment of cortical venous sinus thrombosis.

Presentation

Aspirin is available in combination with multiple other agents, including caffeine, codeine, and dipyridamole. Only formulations containing aspirin alone are discussed further.

- *Trade names*: Disprin®, Nu-Seals®, and Resprin®. Generics are available.
- *Formulations*: aspirin is available as a dispersible tablet, enteric-coated tablet, standard tablet, and suppository. Tablets: 75 mg, 81 mg (USA),

300 mg, 325 mg (USA), 500 mg (USA), and 650 mg (USA) doses.
Suppository: 300 mg and 600 mg.

Mechanism of action

Aspirin irreversibly inhibits COX enzymes. This reduces the formation of the pro-aggregatory molecule thromboxane A2 by platelets, thus reducing the rate of further clot formation.

Toxicity and side effects

- *Common—gastrointestinal*: gastrointestinal irritation. *Haematological*: iron deficiency anaemia. *Immunological*: allergic reaction. *Neurological*: tinnitus. *Respiratory*: bronchospasm.
- *Serious—gastrointestinal*: major haemorrhage. *Immunological*: angio-oedema.

Contraindications

- *Absolute*: active peptic ulceration, haemophilia and other bleeding disorders, pregnancy (third trimester), gout, severe hepatic impairment. History of hypersensitivity to aspirin or any other NSAID which includes attacks of asthma, angio-oedema, urticaria, or rhinitis. Severe renal (CrCl <10 mL/min) and severe hepatic impairment.
- *Relative*: concurrent use of NSAIDs or anticoagulants, poorly controlled hypertension (increased risk of intracranial bleeding), in those aged <21 due to increased risk of Reye's syndrome. Use with caution in mild to moderate renal impairment, as it can cause further deterioration in renal function, and the risk of gastrointestinal bleed may be increased.

Use in special populations

- *Elderly*: use with caution, as the elderly are at an increased risk of gastrointestinal bleeding.
- *Pregnancy*: aspirin is associated with anaemia and intrauterine growth retardation, and may increase fetal mortality. It should be used only if benefits outweigh the risk and ideally stopped in the third trimester to reduce the risk of bleeding during delivery.
- *Lactation*: Reye's syndrome is associated with aspirin use by infants with viral infections. Salicylic acid is excreted into breast milk, but at disproportionate higher levels at higher doses. Case reports have linked high-dose use with metabolic acidosis in breastfeeding infants. Daily low-dose aspirin 75–325 mg daily is not associated with detectable salicylic acid in breastmilk and hence this dose can be considered in breastfeeding mothers who require antiplatelet treatment.

Efficacy

See discussion of evidence base in the management of stroke and transient ischaemic attacks in Chapter 4, Cerebrovascular disease, p. 49.

Dosing and monitoring

Dosing

USA: Recommended medical management after ischaemic stroke is 325 mg of aspirin od for 90 days (with 75 mg of clopidogrel concurrently) if significant intracranial atheromatous disease is present or 21 days in the absence of atheromatous disease.

UK: Recommended medical management after ischaemic stroke is 300 mg once daily given for 2 weeks.

Patients with a current or previous history of dyspepsia should be given a proton-pump inhibitor at the same time as aspirin.

Monitoring

FBC and renal function monitoring should be performed regularly in patients at risk of bleeding or renal impairment respectively.

Pharmacokinetics and interactions

Pharmacokinetics

Aspirin is largely absorbed in the small intestines; a small amount of the ionized form is absorbed by the stomach. Bioavailability is 50–75%. T_{max} is 1–2 h. Aspirin is rapidly hydrolysed to salicylate predominantly by the gastrointestinal mucosa and red blood cells. 50–80% of salicylate is bound to plasma proteins. It is predominantly metabolized hepatically by conjugation with glycine. The half-life of salicylate is 3 h at doses of 300 mg—this increases markedly at higher doses. Excretion is predominantly renal—75% as salicyluric acid.

Interactions

See Table 24.5.

Table 24.5 Interactions of aspirin

Medications which alter aspirin plasma levels	Medications whose plasma levels are altered by aspirin	Pharmacodynamic interactions
Levels decreased: corticosteroids and kaolin. Levels increased: metoclopramide	Levels increased: methotrexate and zafirlukast	With acetazolamide: increased risk of toxicity with high-dose aspirin With clopidogrel, corticosteroids, coumarins, iloprost, NSAIDs, SSRIs, and venlafaxine: increased risk of bleeding Probenecid, spironolactone, sulfinpyrazole: aspirin antagonizes their effects. With valproate and phenytoin: aspirin enhances their effects. Varicella zoster vaccines: possible increased risk of Reye's syndrome

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Azathioprine

Azathioprine was developed in the 1950s as a chemotherapeutic agent and was subsequently used in the 1960s as one of the early immunosuppressants for transplantation. It is currently used in a wide range of autoimmune neurological diseases.

Uses

Azathioprine use in neurology is off-label. It is usually indicated in immunosuppressive regimens as an adjunct to basic immunosuppression with corticosteroids, which form the mainstay of therapy. It may also be used in patients who are intolerant to corticosteroids. Common neurological uses are given below:

- Autoimmune limbic encephalitis.
- Bechet's (first-line, chronic).
- Giant cell arteritis (GCA) (second-line, chronic).
- LEMS (first-line, chronic).
- MG (first-line, chronic).
- Neurolupus (first-line, chronic).
- NMO (first-line, chronic).
- PM/DM (first-line, chronic).
- Sjögren's syndrome (first-line, chronic).
- Susac's syndrome.
- Vasculitis.

Presentation

- *Trade names*: Azamune®, Azasan®, and Imuran®. Generics are available.
- *Formulations*: azathioprine is available as oral tablets (Azamune® and Azasan®) and vials of powder for IV infusion (Imuran®). Oral tablet: 25, 50, 75, and 100 mg. Vial: 50 mg.

Mechanism of action

Azathioprine is metabolized into 6-mercaptopurine, which acts both as a purine antimetabolite inhibiting nucleic acid synthesis and as an alkylating agent. This allows the drug to modulate immunological responses by limiting leucocyte proliferation. It also exhibits antineoplastic effects.

Toxicity and side effects

The principal side effect is a dose-related suppression of bone marrow function.

- *Common—Gastrointestinal*: nausea and vomiting. *Haematological*: anaemia, leucopoenia, and thrombocytopenia. *Immunological*: increased risk of infection.
- *Serious—Dermatological*: Kaposi's sarcoma, squamous cell carcinoma, and Stevens–Johnson syndrome. *Gastrointestinal*: gastric ulceration, hepatic impairment (including veno-occlusive disease), and pancreatitis. *Gynaecological*: cervical and vulval cancer. *Haematological*: acute myeloid leukaemia, bone marrow failure, myelodysplastic syndromes, and non-Hodgkin's lymphoma. *Immunological*: hypersensitivity reactions (including acute kidney injury, anaphylaxis, and vasculitis). *Respiratory*: interstitial pneumonitis (reversible).

Contraindications

- *Absolute*: hypersensitivity, severe infections, severe hepatic impairment, bone marrow failure, pancreatitis, and concurrent live vaccination.
- *Relative*: patients with renal disease or mild to moderate hepatic impairment should be given doses at the lower end of the normal range.

Use in special populations

- *Elderly*: this drug has not been studied in the elderly; however, the elderly experience an age-related decline in hepatic and renal function and should be given doses at the lower end of the normal range.
- *Pregnancy*: azathioprine is teratogenic in animals but limited data in human studies suggests that exposure in early pregnancy dose not increase the risks of congenital malformation or preterm delivery. Neonatal leukopenia and thrombocytopaenia have been reported.
- *Lactation*: Azathioprine is probably safe to use whilst breastfeeding. Studies in women taking up to 200 mg OD for SLE and other indications have found very low levels of active metabolites in milk or infant serum. Mild asymptomatic neutropenia in infants has been reported and could be monitored for. Not breastfeeding in the first 4 h post oral administration will likely significant reduce the infant's dose.

Efficacy

See under separate conditions in the relevant chapters.

Dosing and monitoring

Dosing

An oral dose of 1–3 mg/kg daily is typically used in autoimmune conditions. A usual starting dose is between 50–100 mg/day. This should be taken with meals. The dose is then gradually increased over weeks, with FBC monitoring, to achieve optimum symptomatic control, whilst minimizing the risk of significant cytopenia.

Monitoring

Thiopurine methyltransferase (TPMT) metabolizes azathioprine and has reduced enzyme activity in up to 10% of the population. TMPT levels should be measured in all patients prior to treatment initiation. Regular FBC monitoring is required during treatment. This should be weekly for the first 2 months and can then be done at least every 3 months thereafter. Patients should be advised to seek help if they develop a fever, sore throat, bruising, bleeding, or signs of infection. They should also be warned about the increased risk of skin cancer. Their skin should be examined at regular intervals. Withdrawal of this drug can lead to severe relapses in disease and should be done gradually. Chickenpox can be fatal in the immunocompromised, and patients should be advised to seek medical help if they are not immune and become exposed.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of azathioprine is highly variable: 30–90%. Plasma levels peak within 2 h of administration. The drug is rapidly distributed, with a maximum of 30% binding to plasma proteins. Azathioprine is a prodrug; it is metabolized by both the liver and kidneys to the principal active metabolite 6-mercaptopurine. The plasma half-life of azathioprine is 30–80 min, and that of 6-mercaptopurine 3–5 h. 6-mercaptopurine is subsequently metabolized by several different enzymes, including TMPT and xanthine oxidase, into inactive metabolites. Around 50% of a given dose is excreted in the urine in the first 24 h, and 12.6% can be found in the stool at 48 h. Only a small amount of <2% is excreted as unchanged drug.

Interactions

See Table 24.6.

Table 24.6 Interactions of azathioprine

Medications which alter azathioprine plasma levels	Medications whose plasma levels are altered by azathioprine	Pharmacodynamic interactions
Increased levels: allopurinol	Decreased levels: warfarin	With ACE inhibitors, aminosalicylates, NSAIDs, ribavirin, sulfamethoxazole, and trimethoprim: the myelosuppressive effects are increased. With febuxostat: the manufacturer advises against concomitant use

Baclofen

Along with tizanidine, it remains a first-line treatment for spasticity of both cerebral and spinal origin. Oral baclofen has low CSF penetrance, and thus side effects can be problematic for many patients at the doses required for therapeutic response. Intrathecal infusion of baclofen (ITB) has since become a widely adopted treatment for both chronic spasticity and dystonia.

Uses

1. Oral baclofen.

Licensed uses

In the UK

- *Spasticity*: baclofen is licensed for the treatment of voluntary muscle spasticity secondary to cerebral disorders (such as meningitis, stroke, and traumatic head injury) and spinal disorders (including MS and motor neuron disease (MND)) in individuals of all ages.

In the USA

- *Spasticity*: baclofen is licensed for the treatment of spasticity associated with spinal cord diseases and injuries, including MS (but not stroke, cerebral palsy, or PD), in individuals of all ages.

Off-label uses

- Bladder spasticity and dystonia (particularly useful in segmental forms and childhood dystonic gait).

2. Intrathecal baclofen.

Licensed uses

In the UK/USA

- *Spasticity*: for use by specialist units to treat severe, chronic spasticity of cerebral or spinal origin unresponsive to oral therapy or if side effects of oral therapy not tolerated in individuals over the age of 4.

In the UK, patient selection criteria are clearly defined by commissioning boards.

Off-label uses

- Severe generalized dystonia (particularly if concomitant severe spasticity).

Presentation

- *Trade names*:
  1. oral: Gablofen®, Lioresal®, and Lyflex®. Generics are available.
  2. intrathecal: Baclofen Aguetant, Gablofen® and Lioresal®. Generics are not available.
- *Formulations*: baclofen is available as an oral solution and tablet. Oral solution: 5 mg/5 mL oral solution in 150 mL and 300 mL bottles. Tablet: 10 mg and 20 mg. Intrathecal baclofen is available as a solution for

injection in 1 mL ampoules of 50 micrograms/mL (for test doses), and 5 mL (2 mg/mL) and 20 mL (500 micrograms/mL) ampoules (for use with implantable pumps).

Mechanism of action

Baclofen exhibits affinity for both pre- and post-synaptic $GABA_B$ receptors and acts predominantly at the spinal cord level. Activation of presynaptic $GABA_B$ receptors leads to axonal hyperpolarization. This reduces the chance of depolarization and subsequent exocytosis of excitatory neurotransmitters into the synaptic cleft. Stimulation of post-synaptic $GABA_B$ receptors similarly leads to cell hyperpolarization, thus preventing action potential propagation.

Intrathecal delivery is via an adjustable, implantable pump (typically situated in the lateral abdominal wall) with a tunnelled spinal catheter. The most frequently used pump devices are the battery powered SynchroMed® series (typical battery lifespan is 7 years). This method of delivery allows maximal concentration of baclofen to be achieved at the target spinal $GABA_B$ receptors, while minimizing systemic side effects.

Toxicity and side effects

- *Common—Cardiovascular*: decreased cardiac output, hypotension. *Dermatological*: hyperhidrosis, rash, urticaria. *Endocrine*: hyperglycaemia. *Gastrointestinal*: constipation, diarrhoea, LFT derangement, nausea, retching. *Musculoskeletal*: myalgia. *Neurological*: ataxia, confusion, dizziness, headache, muscle weakness, nystagmus, sedation. *Ophthalmological*: accommodation disorders, visual impairment. *Psychiatric*: depression, euphoria, hallucinations, insomnia, nightmares. *Urological*: dysuria, enuresis.
- *Serious*: serious adverse effects are thought to be more common with spasticity secondary to stroke. *Neurological*: paradoxical increased spasticity and seizures. *Respiratory*: respiratory depression.

Intrathecal

- *Test dosing*: nausea, vomiting, dizziness, headache, transient hypotonia, sedation, and urinary retention are common. Rarely, even small doses can induce coma; hence resuscitation facilities are required.
- *Pump implantation*: common postoperative side effects include headache, constipation, and CSF leakage or collection. The risk of bacterial meningitis is ~1%. The long-term risk of localized pump infection is ~10% (subfascial pumps may be less prone to infection than subcutaneous ones). There are several case reports of catheter tip granulomas which can cause neurological impairment.
- *Overinfusion*: typically occurs following errors with pump refilling or reprogramming, causing overdose. Clinical signs develop rapidly and include sedation, hypotonia, hypotension, bradycardia, and respiratory depression. Convulsions, rhabdomyolysis, and prolonged coma can result. Treatment is supportive, in an intensive care environment, while the pump is immediately stopped and drained.

Therapeutic CSF drainage can be performed, although its efficacy is uncertain.
- *Underinfusion*: typically occurs due to catheter blockage/disconnection (common—especially in the first year) or depletion of baclofen, rarely due to pump malfunction. This can lead to the potentially fatal baclofen withdrawal syndrome within hours or days (clinically resembling NMS)—hyperthermia, muscle spasm, rigidity, and later convulsions, status epilepticus, rhabdomyolysis, coagulopathy, and multiple organ failure. Early symptoms include pruritus, paraesthesia, and hypotension. Treatment is supportive. Intrathecal infusion should be restored as soon as possible—PO baclofen and IV benzodiazepines can be used as a temporary measure. Electromagnetic interference can also cause a transient pump stall, potentially leading to underinfusion—this is known to occur during MRI. While this does not exclude ITB patients from undergoing MRI, patients should have their pump status checked immediately after scanning.
- *Drug-related side effects*: systemic effects are not totally eliminated with intrathecal therapy.

Contraindications

- *Absolute*: hypersensitivity to baclofen, active peptic ulceration, porphyria.
- *Relative*: use with caution in patients with severe psychiatric disorders (possible exacerbation), concomitant antihypertensive therapy (risk of profound hypotension), epilepsy (may lower seizure threshold), history of peptic ulceration (stimulates gastric acid secretion), end-stage renal failure (risk of overdose), and urinary sphincter hypertonia (risk of acute retention). Baclofen is predominantly renally excreted; use smaller doses, e.g. 5 mg/day, in renal impairment. If eGFR is <15 mL/min/1.73 m^2, use with caution, only if potential benefits exceed risks. In hepatic impairment, use with caution, but no dose adjustment is routinely recommended.

Use in special populations

- *Elderly*: older patients may be more prone to sedation and hypotension; thus, close monitoring and careful dose titration are advised.
- *Pregnancy*: baclofen crosses the placental barrier. While there have been no reports of teratogenic effects in humans, use in the first trimester should be avoided where possible. Use with caution in later pregnancy, as use may be associated with withdrawal symptoms in the infant.
- *Lactation*: baclofen is secreted in breast milk in minute quantities (~3–4%of the maternal weight-adjusted dose). No adverse events have been reported. Infants should be monitored for sedation and withdrawal.

Efficacy

1. Oral.

Numerous low-quality trials have investigated the use of baclofen in the treatment of dystonia and spasticity. True meta-analysis of these trials has proven difficult, due to their heterogeneity, with regard to both the test subjects' underlying conditions and the outcome measures used. There is therefore a lack of robust comparative evidence to support the use of baclofen over other agents.

- *Dystonia*: baclofen has been found to be effective in the treatment of dystonia in retrospective studies and case reports, with a greater effect in children than adults. One series (n = 358) assessed the effectiveness of baclofen on patients following initial treatment with an anticholinergic. Here, 20% of patients with various forms of dystonia had a good response to oral baclofen. Factors associated with a good response were those with mild to moderate dystonia and age <20.
- *Spasticity*: a 2004 systematic review investigated whether baclofen was superior to placebo. Out of 14 trials from 1977 to 2000, ten found in favour of oral baclofen vs. placebo for spasticity of various aetiologies (but predominantly MS). Outcome measures included improvements in Ashworth scores in some trials, but most used non-validated outcomes. A 2003 review of antispasticity agents used in MS found no difference in efficacy between baclofen and diazepam. A 1998 meta-analysis of ten previously unpublished trials found baclofen to be of comparable efficacy to tizanidine and diazepam (participants were predominantly MS patients).

2. Intrathecal.

A number of case series have shown impressive improvements in Ashworth scores in patients previously unresponsive to oral therapy. Placebo-controlled trials are lacking, due to the nature of the delivery system; however, one Dutch centre has conducted a small RCT (the two study arms commenced ITB 6 months apart) finding in favour of ITB vs. continuing oral therapy. A recent RCT showed higher achievement of treatment goals with intrathecal baclofen versus placebo in 31 (17 ITB) patients with severe dyskinetic CP related dystonia. Many centres have published positive long-term follow-up data over the last two decades, and this is increasingly being supported by favourable meta-analyses of functional outcomes. The cost/benefit ratio has been explored extensively and appears favourable for patients with good carer support who exhibit poor response to oral therapy.

Dosing and monitoring

Dosing

1. Oral baclofen

- *Dystonia*: start treatment at 5 mg at night and increase the dose by 5 mg every week to reach 10 mg tds. The usual maintenance dose ranges from 60 to 100 mg/day.
- *Spasticity*: start treatment at 5 mg tds. This can be increased by 5 mg tds at 3-day intervals.

Symptoms are usually controlled at doses of 20 mg tds or less. Maximum total daily dose should not exceed 100 mg. Discontinuation is advised if no response occurs after 6 weeks of therapy.

Administration with meals may reduce gastrointestinal side effects. Regular review of therapeutic response and sedative side effects is required during the initial titration period.

Discontinuation Abrupt cessation of baclofen can lead to rebound spasticity, as well as physiological and psychiatric symptoms of withdrawal, particularly following long-term therapy. Therefore, a gradual downward tapering of dosage over a period of at least 7–14 days is advised.

Monitoring

No routine monitoring is required.

2. Intrathecal baclofen

(Below are the manufacturer's guidelines. Some centres may have their own protocols.)

Test dosing All patients require test dosing before consideration for long-term ITB. An initial 25-microgram dose is administered via a lumbar puncture over a minimum of 1 min in a fully monitored environment. Further test doses can be administered at 24 h intervals, increasing in 25-microgram increments up to a maximum of 100 micrograms. Patients should be observed continuously for a reduction in spasticity lasting 4–8 h.

Ongoing dosing Following pump implantation, the initial daily dose is as follows:

- *patients with a response to test dose lasting <12 h*: double the initial test dose infused continuously over a 24 h period.
- *patients with a response to test dose lasting >12 h*: the initial test dose infused continuously over a 24 h period.

Titration Daily infusion doses should be increased by 10–20% no more quickly than every 24–48 h, until a satisfactory response has been achieved. Patients with spasticity of cerebral origin may require more cautious up-titration. Maintenance doses of 300 micrograms/24 h are typical in patients with cerebral spasticity. Patients with spinal spasticity often require higher doses of up to 800 micrograms/24 h. Doses of up to 2 mg/24 h have been used.

Patients should be well established on a suitable daily infusion dose, before more complex regimes, such as overnight boosting, are attempted.

Discontinuation Discontinuation should proceed by gradual downward titration of the daily infused dose to prevent baclofen withdrawal syndrome.

Monitoring

Patients require regular follow-up for reservoir refilling and often need a gradual increase in the daily infusion dose over time. Again, this should proceed in 10–20% increments.

Pharmacokinetics and interactions

Pharmacokinetics

The oral preparation has a bioavailability of ~100%. Peak plasma concentrations occur at 2–3 h. Ingestion with food does not affect bioavailability. Approximately one-third of the absorbed medication is bound to serum proteins. Baclofen penetrates the blood–brain barrier to reach the CSF where concentrations are 10–12% of the serum level. The half-life is 3–4 h in the serum, and 5 h in the CSF. ~15% of an oral dose undergoes deamination in the liver to form a pharmacologically inactive metabolite. The remaining 85% is excreted unchanged in urine.

With regard to intrathecal pharmacokinetics, there is significant inter-patient variability. At typical intrathecal infusion rates, steady-state CSF concentrations are reached within 1–2 days and vary between 100 and 1000 ng/mL. Plasma concentrations are typically <5 ng/mL. Bolus-dose half-life is in the region of 1–4 h. CSF clearance is ~30 mL/h.

Interactions

See Table 24.7.

Table 24.7 Interactions of baclofen

Pharmacodynamic interactions
With antihypertensives: increased risk of hypotension
With CNS depressants, e.g. alcohol: potential for increased sedative effects
With dopaminergics and lithium: avoid levodopa, as confusion, hallucinations, and headaches can be profound; lithium can aggravate hyperkinetic symptoms
With TCAs: can cause muscle hypotonia and increased sedative side effects

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Betahistine

Betahistine hydrochloride was first used in the treatment of Ménière's disease in the 1960s. It is a histamine analogue which acts as a H1 receptor agonist and a H3 receptor antagonist. It remains widely used in Europe for the management of vertigo and other symptoms associated with Ménière's disease.

Uses

Licensed uses

In the UK

- *Vertigo*: betahistine is licensed for the treatment of Ménière's disease in individuals aged 18 years and older.

In the USA

- Betahistine is not licensed for use in the USA.

Off-label uses

- Vertigo of vestibular origin.

Presentation

- *Trade names*: Serc®. Generics are available.
- *Formulations*: betahistine is available as a tablet in 8 mg, 16 mg, and 24 mg doses.

Mechanism of action

The mechanism of action for betahistine is only partially understood. Betahistine is a weak H1 receptor agonist and a strong H3 receptor antagonist. Agonistic effects at H1 receptors on the pre-capillary sphincter in the stria vascularis of the inner ear result in vasodilatation and increased vascular permeability, thereby reducing the associated pressure of endolymphatic hydrops seen in Ménière's disease. H3 receptors are inhibitory autoreceptors; thus, the antagonism of betahistine at this site is believed to stimulate histamine release, thereby increasing the action of histamine at H1 receptors and reducing hydrostatic pressure within the inner ear.

Toxicity and side effects

- *Common—Gastrointestinal*: dyspepsia and nausea. *Neurological*: drowsiness and headache.
- *Serious—Cardiovascular*: palpitations. *Immune System – anaphylaxis. Dermatological*: hypersensitivity reactions, angio-oedema, and Stevens–Johnson syndrome have been reported. *Gastrointestinal*: peptic ulcer disease.

Contraindications

- *Absolute*: hypersensitivity to betahistine or its excipients and phaeochromocytoma.
- *Relative*: bronchial asthma, peptic ulcer disease, severe hypotension, and patients with pre-existing urticaria, rashes, or allergic rhinitis, as all of these conditions may be exacerbated by betahistine. No dosage adjustment is routinely recommended for patients with hepatic or renal impairment in the product literature—use with caution.

Use in special populations

- *Elderly*: no dose adjustment is required. Use with caution, as the elderly are more prone to side effects and have an age-related impairment in hepatic and renal function.
- *Pregnancy*: animal reproductive studies have shown no adverse effects; however, as a precaution, manufacturers advise avoiding use during pregnancy due to lack of adequate data.
- *Lactation*: it is not known if betahistine is excreted in breast milk. Animal studies have shown post-partum effects only with very high doses. As a precaution, the manufacturers advise avoiding use in nursing mothers.

Efficacy

Betahistine is commonly used for the treatment of Ménière's disease in the UK; however, supporting evidence for its use is of poor quality, and, for this reason, betahistine is not licensed in the USA. A 2011 Cochrane review of seven trials (243 patients with Ménière's disease) found that there was insufficient evidence of any beneficial effect of betahistine on symptoms. Although most trials suggested a reduction in vertigo (and, to a lesser extent, tinnitus), the Cochrane review concluded these effects may have arisen due to bias in the methodology of the trials. Other reviews since 2011 have found similar results.

Dosing and monitoring

Dosing

Initial dose is 8–16 mg tds with food. The usual maintenance dose is 24–48 mg/day. The daily dose should not exceed 48 mg.

Monitoring

None is required.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of betahistine is ~100%. T_{max} is 1 h; this is delayed with food co-ingestion. Binding with plasma proteins is <5%. It is rapidly and almost completely metabolized to 2-pyridylacetic acid, an inactive metabolite, by the liver. Eighty-five per cent is excreted in the urine as inactive metabolites. The elimination half-life of 2-pyridylacetic acid is ~3.5 h.

Interactions

See Table 24.8.

Table 24.8 Interactions of betahistine

Medications which alter betahistine plasma levels	Pharmacodynamic interactions
Levels increased: MAOIs	With antihistamines: theoretically, the effects of betahistine are antagonized by antihistamines

References

James A, Burton MJ. Betahistine for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2001;1:CD001873. (Last amended 2020)

β-interferon (Interferon beta)

IFN-β1b was the first drug demonstrated to reduce relapse rates in RRMS. The pivotal trial was published in 1993, and IFN-β remains a first-line therapy in RRMS to this day. Its advantages are an established history of use and experience in MS over the last 20 years. It does, however, require regular injections and is often associated with flu-like side effects, making newer oral disease-modifying agents a more attractive alternative for many.

Uses

Licensed uses

In the UK/USA

- *RRMS*: Avonex®, Betaferon®/Betaseron®, Extavia®, Plegridy® and Rebif® are licensed for patients with RRMS. In the UK, this requires two or more relapses in the previous 2 years (or 3 years for Avonex®), without evidence of disease progression between relapses.
- *Clinically isolated syndrome*: these drugs are also licensed for patients with a single demyelinating event with an active inflammatory process. In the USA, MRI features consistent with MS are required. In the UK, diagnoses other than MS must be excluded, the event must be severe enough to warrant treatment with IV corticosteroids, and the patient should be deemed to be at high risk of developing clinically definite MS. Rebif® therapy is licensed for this use in the UK.

Off-label uses

- None.

Presentation

- *Trade names*: Avonex®, Betaferon®/Betaseron®, Extavia®, Plegridy®, and Rebif®. Generics are not available.
- *Formulations*: IFN-β1a is available as a solution for injection in cartridges, pre-filled syringes, or vials. Cartridges (Rebif®): 22 and 44 micrograms. Pre-filled syringes and vials (Avonex®): 30 mg, (Plegridy®): 63, 94, and 125 micrograms. IFN-β1b is available as vials of powder with solvent. Vials (Betaferon®/Betaseron® and Extavia®): 300 mg.

Mechanism of action

IFN-β is a cytokine produced by macrophages and fibroblasts. Exogenous IFN-β can be further subdivided into IFN-β1a or 1b. These differ structurally through subtle variations in amino acid sequence and glycosylation state. They bind to type I IFN receptors and induce a multitude of transcriptional changes. These result in reduced expression of various pro-inflammatory cytokines and upregulation of the expression of anti-inflammatory cytokines. Plegridy® is a pegylated version of interferon beta-1a, whose pegylated structure results in a slower rate of metabolism and hence once fortnightly dosing, compared to a higher rate of administration with alternative interferon based drugs. The exact mechanism of therapeutic effects in patients with MS is not yet understood.

Toxicity and side effects

- *Common—dermatological*: increased sweating, injection site pain/erythema, flushing, and a rash. *Endocrine*: elevated serum potassium, thyroid dysfunction. *Gastrointestinal*: anorexia, diarrhoea, deranged LFTs, nausea, and vomiting. *Haematological*: decreased lymphocyte and neutrophil counts. *Immunological*: fever, flu-like symptoms, malaise, and night sweats. *Musculoskeletal*: arthralgia, back pain, muscle cramping/stiffness, and myalgia. *Neurological*: headache, hypoesthesia, and muscle spasticity. *Psychiatric*: depression and insomnia. *Respiratory*: rhinorrhoea.
- *Serious—cardiovascular*: congestive cardiac failure. *Dermatological*: injection site infection/necrosis. *Gastrointestinal*: hepatitis and pancreatitis. *Haematological*: capillary leak syndrome if pre-existing monoclonal gammopathy and thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) have been reported. *Immunological*: anaphylaxis. *Neurological:* seizures have been reported. *Psychiatric:* suicide, psychosis.

Contraindications

- *Absolute*: Hypersensitivity to natural or recombinant interferon, severe depression, suicidal ideation, and specifically for IFN-β1b (Betaferon®/Betaseron® and Extavia®) decompensated liver disease.
- *Relative*: caution should be used in patients with any hepatic impairment and severe renal impairment, in whom close monitoring is advised.

Use in special populations

- *Elderly*: IFN-β has not been extensively studied in the elderly. However, this group has an age-related deterioration in hepatic and renal function; hence caution is required.
- *Pregnancy*: A large European registry of 948 pregnancy reports did not find an increased rate of congenital anomalies or spontaneous abortions in patients taking IFN-β before conception or during pregnancy. The product literature recommends IFN-β should be stopped when pregnancy is confirmed. In practice the pros and cons of continued therapy should be considered on an individual basis (see Chapter 6, Multiple sclerosis and related disorders).
- *Lactation*: IFN-β levels in breastmilk are very low and it is poorly absorbed orally, no adverse infant effects have been reported and hence it is generally considered safe to use whilst breastfeeding.

Efficacy

An approximate decrease in the annual relapse rate (ARR) of 30% was shown for IFN-β1b (Betaferon®/Betaseron®), IM IFN-β1a (Avonex®), and SC IFN-β1a (Rebif®) in the pivotal trials (IFN-MS Study Group, MSCRG, and PRISMS). Several comparison trials have suggested slight superiority of high-dose, frequently administered SC IFN-β, compared to lower-dose, weekly IM IFN-β (INCOMIN and EVIDENCE trials). However, development of neutralizing antibodies appears lower with IM IFN-β, possibly negating this effect. Broadly, the efficacy of all injectable agents is considered comparable.

Dosing and monitoring

Dosing

Avonex® is a once-weekly IM dose of 30 micrograms. To reduce the incidence and severity of flu-like side effects, it is recommended to start and increase the dose by 7.5 micrograms a week. Rebif® is a three times per week SC dose of 22 or 44 micrograms. Betaferon®/Betaseron® and Extavia® are given SC on alternate days at a dose of 250 micrograms. This dosing should be titrated up as: 62.5 micrograms for the first three doses, 125 micrograms for the second three doses, 187.5 micrograms for the next three doses, and then 250 micrograms from then onwards. Plegridy® is administered by a pre-filled pen for SC injection. The first dose is 63 micrograms, the second at day 14 is 94 micrograms and the third at day 28 is 125 micrograms. Fortnightly 125 microgram injections are the usual maintenance dose. Use of analgesics on treatment days may help mitigate some of the flu-like symptoms.

Monitoring

FBC and LFT monitoring is required before and during therapy at 1 and 3 months, and then 6-monthly. Elevation of liver enzymes of five times the upper limit of normal or with clinical symptoms of hepatic impairment should prompt dose reductions or treatment cessation. TFT and immunoglobulin levels should be checked prior to initiation. Thyroid function should also be monitored periodically, especially if patients have developed symptoms of thyroid dysfunction. Practices of monitoring neutralizing antibodies against IFN-β vary. Some specialists advocate routine measurement, and others only when clinical response to treatment is suboptimal. No data exist to support the need for a washout period before starting alternative immunomodulatory therapy. It is generally stopped for 4–6 weeks before initiating natalizumab treatment, but no washout period is necessary if switching to glatiramer acetate or fingolimod.

Pharmacokinetics and interactions

Pharmacokinetics

IM IFN-β1a demonstrates peak activity between 5 h and 15 h and has a bioavailability that varies with injection site of ~40%. SC IFN-β1a has a peak serum concentration at 3 h, and SC IFN-β1b has a peak serum concentration at 1–8 h. The absolute bioavailability of SC IFN-β1b is ~50%. After multiple doses of SC IFN-β1b, there are no increases in serum concentration. The metabolism of IFN-β is poorly described; it is metabolized and excreted by both the liver and the kidneys. The half-life is highly variable between preparations and can be between 10 h and 70 h. Pegylated interferon (Plegridy®) reaches T_{max} at 1–1.5 days post-dose and has a half-life of 78 +/– 15 h, ~2× longer than non-pegylated interferon beta-1a.

Interactions

None.

References

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Rudick RA, Goodkin DE, Jacobs LD, *et al*.; The Multiple Sclerosis Collaborative Research Group (MSCRG). Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. *Neurology* 1997;49(2):358–63.

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The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43(4):655–61.

Bevacizumab

Bevacizumab is an anti-angiogenic medication. In the context of neuro-oncology, its use is predominantly in the treatment of metastatic solid organ tumours, although the FDA have extended its labelling to treatment-refractory glioblastoma.

Uses

Licensed uses

In the UK/USA

- *Metastatic disease*: bevacizumab is licensed as part of a multi-agent chemotherapy regime in the treatment of metastatic malignancies, including colorectal, non-squamous non-small cell lung, and renal cancer, in individuals aged 18 years and older.

In the USA

- *Glioblastoma (recurrent)*: bevacizumab is licensed as a second-line, single-agent therapy in individuals aged 18 years and older with progressive disease.

Off-label uses

- Meningioma and radiation necrosis.

Presentation

- *Trade names*: Alymsys®, Avastin®, Aybintio®, Oyavas® and Zirabev®. Generics are not available.
- *Formulations*: bevacizumab is available as a concentrate for IV infusion at 25 mg/mL in 100 and 400 mg vials.

Mechanism of action

Bevacizumab is a humanized monoclonal antibody, which selectively binds all isoforms of VEGF, preventing binding to its receptors VEGFR-1 and 2. The VEGF pathway mediates angiogenesis and vascular permeability. As a highly vascularized tumour, glioblastoma requires high levels of angiogenesis to maintain rapid growth. Blockade of this pathway is thought to inhibit tumour growth and reduce vascular permeability, thereby minimizing peritumoural vasogenic oedema. A lack of specificity for neoplastic tissues is responsible for much of its adverse event profile.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension is very common and dose-dependent. Congestive heart failure and supraventricular tachycardia are common. *Dermatological*: dry skin, delayed wound healing, exfoliative dermatitis, palmar–plantar erythrodysaesthesia syndrome, and skin discoloration. *ENT*: epistaxis and rhinitis. *Gastrointestinal*: anorexia, change in bowel habit, nausea, stomatitis, and vomiting. *Haematological*: anaemia, leukopenia, and thrombocytopenia. *Musculoskeletal*: arthralgia, muscular weakness, and myalgia. *Neurological*: dysarthria, headache, fatigue, peripheral sensory disturbance, and syncope. *Ophthalmological*: mild epiphora and optic nerve dysfunction. *Renal*: proteinuria, usually not associated with renal dysfunction, although nephrotic syndrome was identified in up to 1.4% of patients, and UTIs. *Respiratory*: dyspnoea.
- *Serious—cardiovascular*: arterial thromboembolism, deep vein thrombosis, and haemorrhage. *Dermatological*: necrotizing fasciitis can develop in poorly healing wounds. *Endocrine*: risk of ovarian failure in premenopausal women is ~40%. This is reversible after treatment discontinuation in the majority (86%). *Gastrointestinal*: abdominal perforation can occur. The highest incidence is in patients treated for colorectal cancer where the likelihood of abscess, fistula development, or perforation was up to 2.7%. Ileus and intestinal obstruction are other potentially serious side effects. *Immunological*: anaphylactic reactions. *Musculoskeletal*: osteonecrosis of the jaw. *Neurological*: CVA and posterior reversible encephalopathy syndrome.

Contraindications

- *Absolute*: hypersensitivity to any active constituent of the medication, and pregnancy.
- *Relative*: caution in patients with intra-abdominal inflammatory conditions, fistulae, poorly controlled congestive heart failure, or hypertension, and patients with previous history of arterial or venous thromboembolism. Due to poor wound healing and the potential risk of necrotizing fasciitis, bevacizumab should be stopped, ideally for at least 28 days, prior to elective surgery. Bevacizumab should be used with caution in patients with poor dental health or using bisphosphonates, due to the potential risk of osteonecrosis of the jaw.

No specific dose adjustments are required in renal or hepatic impairment.

Use in special populations

- *Elderly*: elderly patients are at higher risk of developing arterial thromboembolic complications and blood dyscrasias, compared to younger patients. They are also more likely to have underlying hypertension and congestive heart failure requiring careful monitoring during treatment.
- *Pregnancy*: animal studies have demonstrated teratogenicity; hence bevacizumab is contraindicated in pregnancy. It should be avoided for at least 6 months prior to conception.
- *Lactation*: no studies have assessed whether bevacizumab is present in human milk; however, human IgG is known to be present. It is advised to avoid breastfeeding for at least 6 months following administration of bevacizumab.

Efficacy

Bevacizumab has demonstrated efficacy in two single-arm, open-label studies investigating previously treated glioblastoma. In both studies, treatment was second line, following prior treatment with temozolomide and radiotherapy. Objective response, based on MRI criteria, was found in 20–26% of patients.

Dosing and monitoring

Dosing

The dosage of bevacizumab varies, depending on body weight, clinical indication, local protocols, and adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines. Doses can vary from 7.5 mg/kg to 15 mg/kg and are usually given at 2- to 3-weekly intervals. The number of cycles depends on the specific chemotherapy regimen.

Monitoring

Prior to initiation of treatment, BP, FBC, and urinary protein should be assessed. These should be monitored throughout treatment, as per local chemotherapy guidelines.

Pharmacokinetics and interactions

Pharmacokinetics

The pharmacokinetics of bevacizumab are linear at doses of 1–10 mg/kg. Metabolism is similar to that of an endogenous IgG molecule, i.e. endothelial cell-mediated proteolysis throughout the body. The half-life is, on average, 18 days for a female patient and 20 days for a male patient. Clearance is accelerated by elevated tumour burden (7%) and low albumin levels (30%).

Interactions

See Table 24.9.

Table 24.9 Interactions of bevacizumab

Pharmacodynamic interactions
With cytotoxics: increased rates/severity of blood dyscrasias
With sunitinib malate: microangiopathic haemolytic anaemia can occur

References

Cloughesy T, Vredenburgh J, Day B, *et al*. Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study. *J Clin Oncol* 2010;28(15):1.

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Botulinum toxin A and B

Clostridium botulinum bacteria produce seven toxins, of which A and B are available commercially, predominantly for their muscle-relaxing properties. Botulinum toxin type A was initially used in the 1980s to treat strabismus. Today, botulinum toxin injections are indicated for the treatment of a wide range of medical conditions, as well as forming the basis of a multi-billion-dollar cosmetic industry.

Uses

Licensed uses (Each brand of toxin has a list of individual licensed uses. If licensing will affect a clinician's practice, they would be advised to review the product literature for that brand).

In the UK

- *Blepharospasm, hemifacial spasm, and idiopathic cervical dystonia*: BTX-A is licensed for the treatment of these conditions in individuals aged 12 years and older.
- *Spasticity*: BTX-A is also licensed for the treatment of focal spasticity in ambulant cerebral palsy individuals aged 2 years and older, and post-stroke spasticity in individuals aged 18 years and older.

In the USA

- *Blepharospasm and strabismus*: BTX-A is licensed for the treatment of these conditions in individuals aged 12 years and older.
- *Spasticity*: BTX-A is licensed for the treatment of upper limb spasticity in individuals aged 18 years and older.

In the USA/UK

- *Bladder dysfunction:* Neurogenic detrusor overactivity with urinary incontinence who are not adequately managed with anticholinergic in individuals aged 5 years in older (USA) and 18 years and older (UK).
- *Cervical dystonia:* BTX-A and B is licensed for the treatment of cervical dystonia in individuals aged 18 years and older.
- *Chronic sialorrhea*: BTX-A is licensed for the treatment of chronic sialorrhea due to neurological disorders in individuals aged 2 years and

older. BTX-B is licensed for the same indication for individuals aged 18 years and older in the USA, but not the UK.
- *Migraine*: BTX-A is licensed for the prophylaxis of chronic migraine in individuals aged 18 years and older.

Off-label uses

- ET, dystonia, and spasticity affecting other body parts, neuropathic pain, tension headaches, and tic disorders.

Presentation

The pharmaceutical preparation comprises the active polypeptide associated with a number of accessory proteins, which differ between manufacturers. Each manufacturer utilizes different quantification systems, all called 'units'. These are preparation-specific and not necessarily interchangeable between brands. For inter-brand conversion ratios see below.

- *Trade names*:
  - medical brands: Type A: Botox® (onabotulinumtoxinA), Daxxify® (daxibotulinumtoxinA), Dysport® (abobotulinumtoxinA), and Xeomin® (incobotulinumtoxinA); Type B: Myobloc® and Neurobloc® (rimabotulinumtoxinB):
  - cosmetic brands: Azzalure®, Bocouture®, Botox Cosmetic®, and Vistabel®. Generics are not available.
- *Formulations*: Botox®, Daxxify® and Xeomin® are available as a powder for reconstitution with sodium chloride solution and subsequent injection in 50 and 100 unit vials (200 unit vials are also available for Botox® and Xeomin®). Dysport® is prepared in the same fashion and is available as 300 and 500 units powder for solution for injection. Neurobloc™ is prepared as solution for injection as 5000 U/mL in a 0.5 mL, 1 mL, and 2 mL vial.
- *Conversion ratios*: Botox® to Xeomin®; 1:1. Botox® or Xeomin® to Dysport®; 3–4:1. Botox® or Xeomin® to Daxxify®; 1:2. Myobloc® and Neurobloc® are the same agent, marketed as a different trade name in the United States (USA) and European Union (EU), respectively. Conversion between type A and B is not standardised . Type B has a proportionately stronger action at autonomic synapses than at the neuromuscular junction (NMJ) when compared to type A, hence this has to be taken into account. Suggested ratios are: Botox®/Xeomin® to Myobloc™ of 1:40 and 1:20 at the neuromuscular junction and autonomic synapse respectively.

Mechanism of action

Botulinum toxin A

BTX-A blocks the release of acetylcholine at the presynaptic NMJ, causing a chemical denervation leading to muscle relaxation. It degrades the synaptosome-associated protein-25 (SNAP-25) protein, which is required for vesicle formation and neurotransmitter release. The mechanism by which BTX-A produces analgesia is under debate. It has been postulated that it induces its analgesic effect independent of its action on muscle tone, possibly by blocking mediators of neurogenic inflammation (e.g. substance P, glutamate, calcitonin gene-related peptide), and thus peripheral and central sensitization to painful stimuli. Different type A products vary depending on the preparations and the presence or absence of accessory proteins. Incobotulinumtoxin (Xeomin®) and Daxibotulinumtoxin (Daxxify®) do not contain any accessory proteins and are stable at room temperature, whilst onabotulinumtoxin (Botox®) and abobotulinumtoxin (Dysport®) contain accessory proteins and hence have to be stored in a fridge. Daxxify® is the most recently approved preparation, having been approved for use by the FDA in 2022. It contains RTP004, which is a short polypeptide that forms a strong electrostatic bond with daxibotulinumtoxinA. This results in a stronger and more prolonged bond with the presynaptic nerve terminal. This results in a longer duration of effect compared to other formulations.

Botulinum toxin B

BTX-B has a similar effect, but a different target, when compared to type A. It cleaves the synaptic vesicle-associated membrane protein (VAMP, also known as synaptobrevin), which is a component of the protein complex responsible for docking and fusion of the synaptic vesicle to the presynaptic membrane, preventing neurotransmitter release, whereas type A toxin cleaves SNAP-25 (see Mechanism of action, earlier) and has similar effects on neurotransmitter release. Type B was discovered after type A and hence has a smaller evidence base. It is licensed only for the treatment of cervical dystonia and sialorrhea where significant improvements similar to that with the type A toxin have been found. No large comparative studies have been published so far looking at differences in the two toxins, although they are generally considered to have a similar clinical effect. Type B is recognized to have more prominent autonomic side effects e.g. dry mouth. In light of this and the markedly stronger evidence base for type A toxin, type B toxin is generally used second-line in patients with resistance/neutralizing antibodies developing during treatment with type A toxin.

Toxicity and side effects

On administration of botulinum toxin, there may be increased electrophysiologic jitter in some distant muscles; misplaced injections may paralyse nearby muscle groups, and excessive doses may paralyse distant muscles. Influenza-like symptoms are common. Local injection site side effects will vary, dependent on the area of the body treated.

- *Common—Dermatological*: dermatitis, ecchymosis, facial oedema. *Gastrointestinal*: dry mouth. *Neurological*: facial droop, headache, muscle weakness. *Ophthalmological*: dry eye, ectropion, entropion, keratitis, ptosis.
- *Serious—Cardiovascular*: arrhythmias, MI. *Dermatological*: anaphylaxis. *Ophthalmological*: angle-closure glaucoma, corneal ulceration/perforation. *Neurological*: aspiration, dysphagia, and seizures.

Contraindications

- *Absolute*: generalized disorders of muscle activity, e.g. MG, infections at injection site.
- *Relative*: history of dysphagia or aspiration.

No dose adjustment is necessary in hepatic or renal failure.

Use in special populations

- *Elderly*: no dose adjustment required.
- *Pregnancy*: there have been no reported side effects when used in pregnancy, although there are limited studies. Low risk of systemic absorption. Use if the benefits outweigh the risks to the fetus.
- *Lactation*: Botulinum toxin is not detected systemically after intramuscular use and hence excretion into breastmilk is unlikely. No studies performed, although one report of an infant successfully breastfed, with no consequences. Generally recognized as safe, as long as the infant does not come into contact with the area of skin injected with BTX-A.

Efficacy

- *Bladder dysfunction: Overactive bladder:* 2 RCTS have shown 100 U BTX-A improved overactive bladder symptoms and quality of life. A recent study followed patients treated with 100 U BTX-A as needed for OAB symptoms over 3.5 years and concluded consistent improvement in OAB symptoms and quality of life without additional safety concerns. It should be noted that most subjects in these studies were women, but it is biologically plausible the results can be extrapolated to men. *Neurogenic detrusor activity with urinary incontinence:* A meta-analysis of 6 RCTs (n = 1915) found that those treated with 200 U or 300 U BTX-A had fewer episodes of urinary incontinence per week compared to placebo as well as improvement in urodynamic parameters. There was no significant difference for episodes of incontinence between the 200 U and 300 U groups. Those treated with BTX-A had a greater incidence of UTI, urinary retention, haematuria, and muscle weakness.
- *Chronic sialorrhea:* An RCT of adult patients with neurological disorders (70% had PD) demonstrated a significant reduction in saliva production vs. placebo ($p = 0.004$) and a significant reduction in the patient's global impression of change score ($p = 0.002$). This lasted up to 4 months post injections. The most common treatment related adverse effects were dry mouth (5.4% and 2.7%, in the 75 U and 100 U groups, respectively) and dysphagia (2.7% and 0% in the 75 U and 100 U groups, respectively).
- *Dystonia*: BTX-A has undergone several open-label trials and RCTs to assess its efficacy in the treatment of focal dystonia. It has been shown to be effective in up to 90% of patients with blepharospasm and, for this reason, is considered first-line. Several RCTs have compared the efficacy of different formulations of BTX-A, with no clear difference noted between the agents. RCTs showing significant improvement in symptoms have also been conducted for cervical, limb, laryngeal, and oromandibular dystonia.
- *Migraine*: Botulinum toxin type A has been demonstrated to be superior to placebo in a 24 week, double-blind, placebo-controlled study. The frequency of headache days per 28 days was reduced by 9 with toxin vs. 6.7 with placebo ($p<0.001$). Botulinum toxin has not been shown to be effective in episodic migraine.

- *Neuropathic pain*: there have been a number of small placebo-controlled trials that demonstrated BTX-A injection could produce significant pain relief in patients with peripheral nerve injury, painful diabetic neuropathy, post-herpetic neuralgia, and post-traumatic neuropathic pain. Analgesic effect usually lasts 3 months. Larger RCTs and meta-analyses are awaited to substantiate these findings.
- *Spasticity*: a 2008 meta-analysis of 13 randomized, placebo-controlled trials totalling 891 subjects concluded that BTX-A was safe and effective in treating focal spasticity of both upper and lower limbs in adults (grade I evidence). Outcome measures included improvements in Ashworth scores, range of motion, cleaning, hygiene, and pain. Use in upper limb spasticity is supported by a recent Cochrane Centre review.

Dosing and monitoring

Dosing

The product literature of the chosen preparation should be consulted for detailed guidance regarding dosing and administration, depending upon the specific indication.

Monitoring

Successful treatment should cause therapeutic benefit within days and last for 3–6 months depending on the preparation.

It is estimated that a small percentage of patients may be resistant to the beneficial effects of BTX-A therapy due to antibody formation against the toxin and/or the associated accessory proteins. This is more likely to occur following frequent administration of high doses. Clinical testing e.g. with frontalis injections should be considered if this is suspected. Other botulinum toxin serotypes may be of use as second-line therapy (BTX-B is currently the only other commercially available serotype).

Pharmacokinetics and interactions

Pharmacokinetics

BTX-A and B are not present in peripheral blood at measurable levels following IM or intradermal injection. Light chains of BTX-A are cleaved by SNAP-25. For most preparations, clinical effect wears off within 3–4 months, daxibotulinum toxinA lasts ~6 months. Antibody formation may lead to deterioration in response.

Interactions

See Table 24.10.

Table 24.10 Interactions of BTX-A (and B)

Pharmacodynamic interactions
With aminoglycoside antibiotics: may potentiate the effect of botulinum toxin.
With anticoagulants and antiplatelet drugs: increased risk of bleeding at the injection site
With anticholinergic drugs: increased anticholinergic side effects
With muscle relaxants: increased risk of muscular weakness

References

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Candesartan

Candesartan is an angiotensin receptor blocker (ARB), commonly used in hypertension and heart failure. Candesartan has been shown to be of some benefit in the prophylaxis of migraine.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- Candesartan is used in the management of heart failure and hypertension. There is no licensed neurological use.

Off-label uses

- Migraine prophylaxis in adults.

Presentation

- *Trade names*: Amias®, Atacand®. Generics are available.
- *Formulations*: candesartan is available as a standard tablet. Standard tablets: 2 mg (only available in the UK), 4 mg, 8 mg, 16 mg, and 32 mg.

Mechanism of action

The mechanism of action for candesartan's effects on migraines is not clear. In general, candesartan functions by preventing the interaction of angiotensin II with the AT_1 angiotensin II receptor subtype. In the CNS, these receptors are present on neurons, cerebral endothelial cells, and astrocytes. Action mediated by these receptors alters cerebral blood flow by several mechanisms: modulation of potassium and calcium receptor activity, increase in cerebral levels of dopamine and 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, and increases in the production of inducible NO synthase. These actions of angiotensin II receptors may be involved in the pathogenesis of migraines.

Toxicity and side effects

- *Common—neurological*: dizziness, headache, vertigo. *Renal*: hyperkalaemia, impaired renal function. *Respiratory*: cough, upper respiratory tract infection, pharyngitis, rhinitis.
- *Serious—gastrointestinal*: deranged LFTs, hepatitis. *Haematological*: agranulocytosis, leucopenia, neutropenia. *Immunological*: angio-oedema.

Contraindications

- *Absolute*: hypersensitivity to candesartan. Candesartan should not be co-administered with aliskiren, a direct renin inhibitor, in patients with diabetes. Avoid in severe hepatic impairment.
- *Relative*: aortic/mitral valve stenosis, hypertrophic cardiomyopathy, and renal artery stenosis. In mild/moderate hepatic impairment and renal impairment, the starting dose is 4 mg. Increase cautiously, with regular monitoring of renal function.

Use in special populations

- *Elderly*: elderly patients may require a smaller starting dose, with slower drug up-titration.
- *Pregnancy*: candesartan is contraindicated in pregnancy. In the second and third trimester, it has been shown to impair fetal renal function, leading to an increased risk of oligohydramnios, lung hypoplasia, skeletal abnormalities, and intrauterine death.
- *Lactation*: there are limited data on the safety of candesartan in breastfeeding. Available evidence suggests candesartan is only present at low levels in breast milk and that infants would be exposed to <1% of weight-adjusted maternal dosage. There is no evidence of harm to the infant. The benefits and risks should be considered if a mother taking candesartan intends to breastfeed.

Efficacy

Candesartan was compared to placebo in a randomized, double-blind cross-over trial of 60 patients. Patients received 16 mg of candesartan or placebo for 12 weeks and then crossed over to the other arm for another 12 weeks. The primary endpoint was the number of headache days over the 12-week period. Secondary endpoints included total migraine days and total headache hours over the same 12-week period. For those on candesartan, there was a statistically significant reduction in total headache days (13.6 vs. 18.5, respectively; p = 0.001), total migraine days (9.0 vs. 12.6, respectively; p <0.001), and total hours with headache (95 vs. 139, respectively; p <0.001). A second randomized, triple-blind, placebo-controlled double cross-over study of 72 patients compared 16 mg candesartan to 160 mg slow-release propranolol and to placebo. Participants received either candesartan, propranolol, or placebo for 12 weeks followed by a 4-week washout period; subjects were then twice crossed over to one of the other arms for two 12 additional week periods. The primary endpoints assessed were number of migraine days, number of headache days, and total headache hours per four weeks. Additionally, the proportion of subjects with a greater than 50% reduction in migraine days was assessed. Compared to placebo, participants on candesartan had statistically significant decreases in total migraine days per four weeks (2.95 vs. 3.53, respectively; p = 0.02), total headache days per four weeks (5.30 vs. 5.97, respectively; p = 0.01), and total headache hours per four weeks (35.1 vs. 43.5, respectively). The total number of responders (>50% reduction in migraine days) was also higher in the candesartan arm compared to placebo (43% vs. 23%, respectively; p = 0.025). The effect size was similar to propranolol.

Dosing and monitoring

Dosing

The dose of candesartan in migraine prophylaxis is 16 mg od. Patients can be started on 4–8 mg od, which can be increased, as tolerated, to 16 mg. In patients with mild/moderate hepatic impairment and renal impairment, the starting dose is 4 mg. The dose should be increased cautiously from there with regular monitoring of renal function.

Monitoring

BP and renal function should be assessed before starting therapy and regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Candesartan is a prodrug and is hydrolysed to its active form on absorption. It is 99% bound to plasma protein and reaches peak plasma concentration at 3–4 h. The bioavailability of the tablet form is 15%. The majority of the drug is excreted unchanged via the kidneys and bile. The elimination half-life is approximately 9 h.

Interactions

See Table 24.11.

Table 24.11 Interactions of candesartan

Medications whose plasma levels are altered by candesartan	Pharmacodynamic interactions
Levels increased: lithium	With ACE inhibitors, calcineurin inhibitors, heparins potassium sparing diuretics, trimethoprim: increased risk of hyperkalaemia With antihypertensives: increased risk of hypotension With NSAIDs: increased risk of renal impairment

References

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Tronvik E, Stovner L, Helde G, *et al*. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003;289(1):65–9.

Cangrelor

Cangrelor is an intravenous ATP analogue, that selectively binds the $P2Y_{12}$ receptor on platelets, inhibiting their activation. It is licensed to reduce thromboembolic complications in patients undergoing percutaneous coronary intervention. It is used in a similar fashion during neurovascular interventions including mechanical thrombectomy and cerebral aneurysm management.

Uses

Licensed uses

In the UK/USA

- There are no licensed neurological uses.

Off-label uses

- Intravenous administration during neurointerventional procedures, including mechanical thrombectomy, stent placement, and flow diversion.

Presentation

- *Trade names*: Kengreal® and Kengrexal®. Generics are not available.
- *Formulations*: Cangrelor is available as a concentrate for reconstitution (50 mg per vial). It is diluted to a concentration of 200migrograms/mL.

Mechanism of action

Cangrelor is an ATP analogue. It selectively binds platelet P2Y$_{12}$ receptor inhibiting their activation and aggregation in a reversible fashion.

Toxicity and side effects

- *Common: Respiratory:* exertional dyspnoea. *Vascular:* ecchymosis, hematoma, increased risk of bleeding, puncture site discharge.
- *Serious: Immunological:* Anaphylaxis, angioedema. *Vascular:* cardiovascular instability, cardiac tamponade, and major haemorrhage.

Contraindications

- *Absolute:* Active bleeding, increased risk of bleeding, history of stroke or TIA, hypersensitivity to cangrelor or its active ingredients, or severe hypertension.
- No dose alterations are required in hepatic or renal impairment.

Uses in special populations

- *Elderly*: No dose alteration is routinely required; however, the elderly are more likely to have a risk factor for bleeding, hence caution is advised in this group.
- *Pregnancy*: No data from human studies is available. Animal studies suggest use may be associated with effects on sperm motility and morphology. Use only if the potential benefits of use outweigh the theoretical risks to the fetus.
- *Lactation*: No data is available regarding the presence of cangrelor in human or animal milk. However, due to its short half-life, it is expected to be minimal.

Efficacy

No RCT has been conducted to investigate the safety or efficacy of cangrelor in patients undergoing any form of neurovascular intervention.

In a pooled analysis, cangrelor was used in 129 patients undergoing acute ischaemic stroke intervention. Complications included asymptomatic ICH (11/87), symptomatic ICH (8/129), retroperitoneal hematoma (2/129), gastrointestinal bleeding (1/129) and intraprocedural thromboembolic complications (1/129). No events of intraprocedural in-stent thrombosis were reported. Although there was a trend towards higher rate of symptomatic ICH with the 4 mcg/kg/min dose compared to <1 mcg/kg/min, no level of significance was reached.

Dosing and monitoring

Dosing

The typical loading dose is 30 mcg/kg bolus IV (rapidly administered; <1 min), followed by 4 mcg/kg/min IV infusion. The infusion should continue for the duration of the procedure, or for 2 h (whichever is longer), up to a maximum of 4 h.

Monitoring

There are no specific monitoring requirements.

Pharmacokinetics and interactions

Pharmacokinetics

C_{max} is reached within 2 min of bolus administration followed by infusion. Cangrelor is 97–98% plasma protein-bound. Cangrelor's half-life is 3–6 min. It undergoes rapid deactivation in the plasma by dephosphorylation. Its metabolism is via dephosphorylation in the plasma, independent of renal or hepatic function. Platelet function is restored within 60 min of infusion cessation. Most of the drug is excreted within 48 h mainly through the urinary (58%) and faecal (35%) route.

Interactions

See Table 24.12.

Table 24.12 Interactions of cangrelor

Pharmacodynamic interactions
With antiplatelets and other agents that increase bleeding risk: increased risk of haemorrhage.

References

Paul A, Entezami P, Holden D, *et al*. Use of intravenous cangrelor and stenting in acute ischemic stroke interventions: a new single center analysis and pooled-analysis of current studies. *Interv Neuroradiol* 2021;27(6):837–42.

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Capsaicin

Capsaicin was first marketed in the UK in 2010. It is derived from chilli peppers and is responsible for the burning sensation when chillies come into contact with the skin and mucous membranes. It is effective in the management of neuropathic pain, its main side effect being localized skin irritation.

Uses

Licensed uses

In the UK/USA

(Licensing is similar.)

- *Neuropathic pain*: The 0.075% capsaicin topical cream is licensed for pain relief in painful diabetic neuropathy and post-herpetic neuralgia in adults. The 0.025% capsaicin topical cream is licensed for pain relief associated with osteoarthritis. In the UK the 8% capsaicin patch is licensed for the treatment of peripheral neuropathic pain in adults, in the USA it is licensed for the treatment of painful diabetic neuropathy or post-herpetic neuralgia.

Off-label uses
None.

Presentation

- *Trade names*: Axsain® (0.075%), Qutenza® (8%), Zacin® (0.025%).
- *Formulations*: topical capsaicin is available as a cream and high-strength patch. Cream: 0.025% and 0.075%. High-strength patch: 8%.

Mechanism of action

Capsaicin binds its receptor TRPV1, a heat-activated calcium channel, on nociceptive neurons, which opens between temperatures of 37°C and 45°C and is responsible for sensing heat and pain caused by excessive temperatures. Capsaicin causes TRPV1 to open at temperatures <37°C, causing a perceived burning sensation. Prolonged exposure to capsaicin depletes nociceptive neurons of neurotransmitters, particularly substance P, leading to reduced pain transmission and an analgesic effect. This is reversible and normal function returns within weeks.

Toxicity and side effects

The main side effects of intense burning and erythema at the application site can be partially reduced by co-administration of lidocaine.

- *Common—cardiovascular*: hypertension. *Dermatological*: abnormal skin odour, bruising, burning sensation, erythema, excoriation, oedema, pruritus, skin dryness, stinging, urticaria, warmth. *Gastrointestinal*: nausea, vomiting. *Musculo-skeletal*: pain in extremity, muscle spasms *Neurological*: hypoaesthesia. *Respiratory*: cough.

Contraindications

- *Absolute*: broken or irritated skin, as well as known previous hypersensitivity reactions to capsaicin or its irritants.
- *Relative*: none.

No dose adjustment is required in hepatic or renal impairment.

Use in special populations

- *Elderly*: no dose adjustment is required in the elderly.
- *Pregnancy*: there have been no reported side effects when used in pregnancy, although there is limited evidence. Generally recognized as safe.
- *Lactation*: there is little information on the use of topical capsaicin during lactation. Systemic absorption from topical application is likely to be minimal. The topical creams are generally recognized as safe, as long as capsaicin does not come into contact with the infant's skin. Do not apply capsaicin to the breast.

Efficacy

A recent systematic review assessed the efficacy of high-dose topical capsaicin (8%) in neuropathic pain. Four studies, involving 1272 participants, demonstrated that 8% capsaicin patches produced significant analgesia over 8- and 12-week periods over low-dose capsaicin (0.04%) in patients with post-herpetic neuralgia, with an NNT of 8.8 (95% CI 5.3–26). Two further studies, involving 801 participants, showed small, but significant, benefits in treating painful HIV neuropathy, with one study showing a NNT of 5.8 (95% CI 3.8–12). Another recent systematic review concluded that low-dose capsaicin cream shows no therapeutic benefit above that of placebo in treating neuropathic pain.

Dosing and monitoring

Dosing

Apply the cream sparingly to the affected area, 3–4 times/day for 8 weeks, then review. Do not reapply more often than every 4 h and avoid application before or after a bath or shower. Avoid all contact with eyes or mucus membranes. For patches, apply a 60 min application of up to four patches. Repeat every 3 months. Do not apply it to the face or close to mucous membranes. Before application of a patch, clip the hairs in the affected area (do not shave) and wash and dry gently. Handle the patch with nitrile gloves (not latex). The patch can be trimmed to the necessary dimensions before application. Pre-treat the area of affected skin and the surrounding 1–2 cm of the skin with a topical anaesthetic.

Monitoring

None required.

Pharmacokinetics and interactions

Pharmacokinetics

Capsaicin is rapidly absorbed by the skin. The exact amount absorbed is unknown. There is little available information about the pharmacokinetics of topical capsaicin.

Interactions

See Table 24.13.

Table 24.13 Interactions of capsaicin

Pharmacodynamic interactions
With ACE inhibitors: can increase the severity of cough

References

Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2012;9:CD010111.

Derry S, Rice ASC, Cole P, *et al*. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2013;2:CD007393.

Carmustine implant

The carmustine implant was first used in the 1990s. It represents a novel approach to bypassing the blood–brain barrier and thus limiting systemic side effects. It is a well-tolerated medication, used as an adjunct to surgery in the management of high-grade gliomas. Plasma levels of carmustine are undetectable, and systemic side effects are rare.

Uses

Licensed uses

In the UK/USA

- *Glioma*: carmustine implants are licensed for use in (1) newly diagnosed high-grade malignant gliomas as an adjunct to surgery and radiation and (2) in the management of histologically confirmed recurrent glioblastoma multiforme where surgical resection is indicated in adult patients.

Off-label uses

- Single brain metastasis, e.g. breast or lung primaries.

Presentation

- *Trade names*: Gliadel® Wafer. Generics are not available.
- *Formulations*: carmustine implants are available as a wafer (1× 14 mm) containing 7.7 mg of carmustine, with polifeprosan, a biodegradable copolymer designed to control carmustine release.

Mechanism of action

Carmustine implants are administered into the lesion site during reductive surgery. Carmustine is a cell cycle non-specific alkylating agent that acts by forming cross-links in both DNA and RNA. This inhibits DNA and protein synthesis. Part of its action may also be mediated by carbamoylation of amino acids.

Toxicity and side effects

Side effects following the use of carmustine implants are, on the whole, consistent with those of patients undergoing craniotomy for malignant gliomas. Systemic side effects, as seen with IV carmustine, are rare.

The main side effects thought to be specific to intralesional administration of implants include: (1) seizures: up to 54% of patients treated with implants for recurrent glioma developed new or worsened seizures in the first 5 postoperative days; (2) brain oedema ~23% vs. 19% for implant and placebo, respectively; (3) impaired neurosurgical wound healing occurs in up to 16% of patients, including wound dehiscence, delayed healing, and wound effusions. As a result of this, the likelihood of developing a CSF leak increased from 0.8% to 5% in the implant group, compared to placebo; (4) abscess/meningitis in 4–5% vs. 1–6% for implant and placebo, respectively; and (5) obstructive hydrocephalus due to migration of the implant into the ventricles.

Other events that appear to be commoner in trials when carmustine implants are used, compared to placebo implants, include:

- *Common—dermatological*: rash, alopecia. *Endocrine*: hyponatraemia. *Gastrointestinal*: nausea and vomiting. *Haematological*: anaemia. *Neurological*: aphasia, confusion, fatigue, headache, hemiplegia. *Psychiatric:* depression *Respiratory*: pneumonia. *Urological*: UTI
- *Serious—respiratory*: pulmonary embolism.

Contraindications

- *Absolute*: previous hypersensitivity to carmustine.
- *Relative*: due to the risk of implant migration into the ventricular system and the potential development of subsequent hydrocephalus, implant insertion into lesional sites communicating with, or in close proximity to, the ventricular system should be avoided.

Dose reduction is not required in hepatic or renal impairment.

Use in special populations

- *Elderly*: there are no safety or efficacy data comparing use of the implants in those aged >65 years to those aged <65 years.
- *Pregnancy*: no studies are available that have recorded the effects of carmustine implant in pregnancy. Carmustine, when used IV, has a documented teratogenic risk; hence the implant should not be used in pregnancy.
- *Lactation*: it is not known whether carmustine is present in human breast milk. The manufacturer advises against breastfeeding with the carmustine implant.

Efficacy

In the management of newly diagnosed high-grade glioma, a double-blind, placebo-controlled clinical trial demonstrated that the carmustine implant increased median survival from 11.6 to 13.9 months ($p = 0.079$), when used as an adjunct to surgery. Within the context of recurrent glioblastoma, a randomized, double-blind, placebo-controlled trial demonstrated improvement in the 6-month survival rate from 36% to 56% ($p = 0.01$).

Dosing and monitoring

Dosing

For the management of both new-onset high-grade glioma and recurrent glioblastoma, ~7–8 implants are used, depending on cavity size. Implants can be broken in half if needed to fit the cavity.

Monitoring

No additional monitoring is required above that routinely used to detect potential postoperative complications.

Pharmacokinetics and interactions

Pharmacokinetics

The exact pharmacokinetics of the carmustine wafer are poorly understood. Implants release carmustine over a period of 5 days and should degrade over 6–8 weeks, provided continuous contact with interstitial fluid. Carmustine delivery to brain interstitial tissues is mediated by both diffusion and a bulk flow mechanism created by vasogenic oedema (most prominent in the first 3 days post-surgery).

The majority of the carmustine component of the implant is excreted renally, with ~62% of radiolabelled carmustine present in the urine at

7 days. The metabolism of interstitial carmustine is not known. In rabbits with implants, no detectable levels were found in the plasma or CSF, suggesting minimal systemic distribution of carmustine.

Interactions

Interactions with other medications have not been formally evaluated. The localized application and low systemic uptake with the implant suggest there are unlikely to be any significant pharmacokinetic interactions.

References

Attenello FJ, Mukherjee D, Datoo G, *et al*. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol* 2008;15(10):2887–93.

Brem H, Piantadosi S, Burger PC, *et al*. Placebo-controlled trial of safety and efficacy of intraoperative delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995;345(8956):1008–12.

Ewand MG, Drem S, Gilbert M, *et al*. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res* 2007;13(12):3637–41.

Cenobamate

Cenobamate was first marketed in the US as an ASM in 2019. It is used as a treatment for focal-onset epilepsy in adults. In the UK it is used as an adjuvant therapy for patients inadequately controlled on two prior anti-seizure medications. In the US it is also used as monotherapy.

Uses

Licensed uses

In the UK

- *Epilepsy*: Cenobamate is licensed for the adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients with epilepsy who are inadequately controlled despite treatment with at least 2 anti-seizure medications.

In the USA

- *Epilepsy*: Cenobamate is licensed for the treatment of partial-onset seizures in adult patients.

Off-label uses

- None.

Presentation

- *Trade names*: XCOPRI ® in the US and Ontozry ® in the EU. Generics are not available.
- *Formulations*: Cenobamate is available as a tablet. Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg.

Mechanism of action

Cenobamate enhances the inactivation of voltage-gated sodium channels. It has also been shown to be a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel.

Toxicity and side effects

- *Common—Dermatologic*: rash. *Gastrointestinal*: constipation, deranged liver function tests, diarrhoea, dry mouth, nausea, and vomiting. *Neurologic*: aphasia, dysarthria, coordination and gait abnormality, headache, memory impairment, nystagmus, somnolence. *Ophthalmologic*: blurry vision, diplopia. *Psychiatric*: confusion, irritability.
- *Serious—Dermatologic*: Drug reaction with eosinophilia and systemic symptoms (DRESS). *Immunologic*: Hypersensitivity.

Contraindications

- *Absolute*: hypersensitivity to cenobamate or its excipients or familial short QT syndrome (a rare genetic syndrome, which is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Suspect if the QTc <340 ms, or <360 ms with personal history of ventricular arrhythmia or family history of short QT syndrome). A dose-dependent decrease in QT interval has been observed with cenobamate, thus it must not be used in familial short QT syndrome. Use in patients with end-stage renal disease undergoing dialysis and severe hepatic impairment is not recommended.
- *Relative:* Dose reductions are recommended in patients with renal impairment. The maximum recommended dose is renal impairment is 300 mg/day. Dose reductions are advised in mild to moderate hepatic impairment. The maximum recommended dose is 200 mg/day.

Uses in special populations

- *Elderly*: Start at a lower dosage to reflect the increased prevalence of decreased renal function, decreased hepatic function, and increased likelihood of pharmacodynamic drug interactions.
- *Pregnancy*: There are no adequate data on the developmental risk associated with the use of cenobamate in pregnant women. In animal studies, administration of cenobamate during pregnancy resulted in adverse effects on development at clinically relevant drug exposures. No information is available on pharmacokinetic changes of cenobamate during pregnancy. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: No information is available on the clinical use of cenobamate during breastfeeding. No studies have been performed to assess the level of cenobamate in breastfed infants. Until more data is available, other medications may be preferred. If used, infants should be monitored for potential side effects such as drowsiness.

Efficacy

As an adjunct in focal-onset epilepsy: In one randomized double-blind placebo-controlled trial the proportion of patients experiencing a 50% or more reduction in seizure frequency was statistically significant—25% for the placebo group compared with 40% for the 100 mg dose, 56% for the 200 mg dose and 64% for the 400 mg dose.

Dosing and monitoring

Dosing

- For the treatment of focal-onset seizures dosage titration is recommended as follows: start treatment at 12.5 mg daily for Week 1 and 2. Then increase to 25 mg daily for Weeks 3 and 4, 50 mg daily for Weeks 5 and 6, 100 mg daily for Weeks 7 and 8, 150 mg daily for weeks 9 and 10, then 200 mg daily for Week 11 and onwards. If needed based on clinical response and tolerability, dose may be increased above 200 mg by increments of 50 mg once daily every two weeks to 400 mg daily maximum.
- ***Monitoring:***
- Baseline CBC, renal and liver function tests should be performed, and these should be monitored for three months and then at least yearly.

Therapeutic drug monitoring: Measurement of plasma levels may be useful in ascertaining compliance. One analysis of cenobamate through plasma concentrations from two randomized control trials showed that a suggested trough plasma concentration reference range (not a target therapeutic range) of 5–35 µg/mL covered 95% of patients who achieved 50% seizure reduction or 100% seizure reduction in these two trials.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is at least 88%. T_{max} is 1–4 h. Neither bioavailability nor T_{max} are affected by food co-ingestion. Steady state is reached in around two weeks of once-a-day dosing. The volume of distribution is 40–50 L. Plasma protein binding of cenobamate is 60% and cenobamate is largely bound to albumin. Cenobamate undergoes extensive metabolism. The primary metabolic pathways are by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5. ~88% is excreted by the renal system and ~5% excreted in faeces, more than 50% of the dose is excreted within 72 h of intake. The half-life in a healthy adult is 50–60 h.

Interactions

See Table 24.14.

Table 24.14 Interactions of cenoba mate

Medications whose plasma levels are altered by cenobamate	Pharmacodynamic interactions
Levels decreased: lamotrigine, carbamazepine, CYP2B6 substrates (bupropion), CYP3A substrates (midazolam), oral contraceptives Levels increased: phenytoin, phenobarbital, desmethylclobazam (active metabolite of clobazam), CYP2C19 substrates (omeprazole)	With medications that cause CNS sedative side effects: e.g. alcohol, antipsychotics, benzodiazepines With medications that can shorten the QT interval: (poorly defined group: lamotrigine and rufinamide)

References

Chung SS, French JA, Kowalski J, *et al.* Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. *Neurol* 2020;94:e2311–22.

Greene SA, Kamin M. Cenobamate trough plasma concentrations in patients with uncontrolled focal seizures achieving 50% and 100% seizure reduction in two randomized clinical studies (1377). *Neurol* 2021;96(15):1377.

Krauss GL, Klein P, Brandt C, *et al*. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. *Lancet Neurol* 2020;19:38–48.

Cyclophosphamide

This alkylating agent was first synthesized for use as a chemotherapeutic agent in the 1950s. It is currently used in a wide range of inflammatory neurological diseases.

Uses

Licensed uses

In the UK/USA

- There are no licensed neurological uses.

Off-label uses

- Acute disseminated encephalomyelitis (ADEM) (severe refractory cases).
- Bechet's disease.
- Multifocal motor neuropathy (MMN) with conduction block (refractory cases).
- Myasthenia gravis MG (refractory cases).
- Neurolupus (first-line, acute, or chronic).
- Neuromyelitis optica (NMO) (second-line, acute, or chronic).
- Polymyositis and dermatomyositis (PM/DM) (refractory cases).
- Primary CNS vasculitis (first-line, acute, or chronic).
- Sjögren's syndrome.
- Susac's syndrome.
- Transverse myelitis (TM) (refractory cases).

Presentation

- *Trade names*: Cytoxan®, and Neosar® Generics are available.
- *Formulations*: cyclophosphamide is available as an oral capsule, an oral tablet (Cytoxan®), a 200 mg/mL solution, or a vial of powder for IV infusion (Cytoxan® and Neosar®). Oral capsule: 25 mg and 50 mg. Oral tablet: 25 mg and 50 mg. Vial of solution: 500 mg, and 1000 mg. Vial of powder: 500 mg, 1000 mg, and 2000 mg.

Mechanism of action

The antineoplastic and immunosuppressant effects of cyclophosphamide are primarily exerted through lymphocyte cytotoxicity. Alkylation and cross-linking of DNA bases in lymphocytes impairs DNA synthesis and transcription, resulting in cell death.

Toxicity and side effects

Acute sterile haemorrhagic cystitis occurs in 10% of patients not **c**o-prescribed mesna (Uromitexan®), an oral antioxidant. Mesna prevents urinary toxicity by interacting with metabolites of cyclophosphamide in the urinary tract.

- *Common—Dermatological*: alopecia and rash. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, nausea, and vomiting. *Genitourinary*: azoospermia and chemical cystitis (in the absence of mesna). *Gynaecological*: amenorrhoea. *Haematological*: leucopenia.
- *Serious—Cardiovascular*: arrhythmia, congestive heart failure, myocarditis, and pericarditis. *Gastrointestinal*: hepatic impairment (including veno-occlusive disease). *Genitourinary*: bladder contractures or fibrosis secondary to chemical cystitis (which can be haemorrhagic) and secondary urothelial malignancy can occur. *Haematological*: bone marrow failure. *Immunological*: anaphylaxis and increased risk of infections and malignancies. *Respiratory*: pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease.

Cyclophosphamide can cause infertility in both men and women. This should be discussed prior to treatment, and oocyte or sperm-preserving procedures discussed, as appropriate.

Contraindications

- *Absolute*: hypersensitivity, urinary outflow obstruction, moderate or severe hepatic impairment (bilirubin >17micromol/L or serum transaminases/ALP >2–3 times the upper limit of normal), and renal impairment (serum creatinine >120micromol/L).
- *Relative*: cyclophosphamide should be used with caution in patients with mild renal or mild hepatic impairment, and dose reductions are necessary.

Use in special populations

💉 of gabapentin. Variations in the use of the two drugs
Elderly: cyclophosphamide has not been studied in this group, but, in light of an age-related deterioration in hepatic and renal function, cautious use with lower doses is often necessary.

- *Pregnancy*: this drug is teratogenic, and pregnancy should be avoided during, and for 1 year after, therapy. Male patients, and their partners, should use contraception during, and for 6 months following, treatment.
- *Lactation*: cyclophosphamide and its metabolites are present in breastmilk for up to 21 days post-administration, possibly longer for large doses, breastfeeding should be avoided with this drug and for up to 6 weeks afterwards.

Efficacy

See relevant conditions in Chapter 7, Other inflammatory disorders of the central nervous system.

Dosing and monitoring

Dosing

Dosing regimens vary between indications and between hospitals. We recommend the reader follows local protocols. A typical regimen (CYCLOPS protocol) for central and peripheral vasculitis is given below.

Vasculitis of the nervous system (central or peripheral): 15 mg/kg/pulse. The first three pulses are given IV at intervals of 2 weeks. Subsequent doses are given 3-weekly (either 15 mg/kg IV or 5 mg/kg PO for 3 days). Remission should be achieved within 3 months, with 3 more months of cyclophosphamide after entry into remission. If remission is not achieved, then further pulses can be given at 3-weekly intervals until remission is reached. Remission must be achieved by 9 months, and total duration of therapy should not exceed 12 months. Three months after remission is achieved, switch to a remission maintenance regimen (e.g. azathioprine). Patients aged older than 60 and with an eGFR <30 mL/min will need dose reductions.

Monitoring

FBC, and hepatic and renal function should be monitored frequently prior to, and regularly during, treatment. In addition, a minimum urine output of 100 mL/h and frequent bladder emptying should be encouraged to avoid cystitis.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of cyclophosphamide is >75%. Serum concentrations peak 1 h post-dose. The drug is rapidly converted to its active metabolites, including acrolein and 4-aldophosphamide, in the liver by mixed function oxidases in hepatic microsomes. Metabolites of cyclophosphamide are excreted into the urine. Up to 25% of the parent compound can be found in the urine. The half-life is 3–12 h.

Interactions

See Table 24.15.

Table 24.15 Interactions of cyclophosphamide

Medications whose plasma levels are altered by cyclophosphamide	Pharmacodynamic interactions
Decreased levels: digoxin. Increased levels: suxamethonium	With clozapine: there is an increased risk of agranulocytosis. With fluconazole, itraconazole, and pentostatin: the side effects are increased

Dabigatran etexilate

Dabigatran was first marketed in the US and UK in 2010. It is an effective anticoagulant, which can be used when there is poor INR control, despite compliance with warfarin therapy, or in patients who are allergic to, or unable to tolerate, warfarin.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: dabigatran is licensed to prevent stroke and systemic embolization in people with non-valvular AF in individuals aged 18 years and older. In the UK, individuals need to score at least 1 point on the $CHADS_2$ VASc score.

Off-label uses

- None.

Presentation

- *Trade names*: Pradaxa®. Generics are not available.
- *Formulations*: dabigatran is available as 75 mg, 110 mg, and 150 mg capsules.

Mechanism of action

Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. Since thrombin (a serine protease) converts fibrinogen into fibrin during the coagulation cascade, its inhibition prevents thrombus development. Dabigatran inhibits free thrombin, clot-bound thrombin, and thrombin-induced platelet aggregation.

Toxicity and side effects

- *Common—Dermatological*: pruritus, rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting. *Haematological*: anaemia. *Immunological*: allergic reaction. *Neurological*: headaches.
- *Serious—Gastrointestinal*: intra-abdominal haemorrhage, hepatitis. *Haematological*: haemorrhage. *Neurological*: intracranial haemorrhage. Premature discontinuation of dabigatran increases the risk of thrombotic events, where possible if dabigatran is discontinued, place the patient on an alternative anticoagulant.

Contraindications

- *Absolute*: dabigatran is contraindicated in people with severe renal impairment (CrCl <30 mL/min UK, CrCl <15 mL/min US), severe liver disease, particularly if the prothrombin time is already prolonged, active clinically significant bleeding, known severe hypersensitivity reaction to dabigatran, those with mechanical heart valves, organic lesions at risk of bleeding, impairment of haemostasis, those already on alternative anticoagulant medication, and hepatic impairment or liver disease expected to have an impact on survival. Concomitant treatment

with systemic ketoconazole, ciclosporin, itraconazole, or tacrolimus is also contraindicated.
- *Relative*: patients deemed to be at high risk of bleeding. In moderate renal impairment (CrCl 30–50 mL/min UK, CrCl 15–30 mL/min US), use a reduced dose of 75 mg bd if patients are deemed to be at high risk of bleeding. No dose adjustment is required in mild renal impairment.

Use in special populations

- *Elderly*: patients have a 31% higher trough concentration if they are aged ≥75 years, compared to subjects aged between 65 and 75 years. Hence, if the thrombotic risk is low and the bleeding risk high, a reduced dose of 75–110 mg bd can be considered, at the clinician's discretion, in those aged 75–80 years. Patients aged ≥80 years should automatically receive this reduced dose.
- *Pregnancy*: toxicity has been demonstrated in animal studies; therefore, it should be avoided, unless essential.
- *Lactation*: Dabigatran is poorly excreted into breast milk. Limited studies have suggested very small quantities are present in infant serum following maternal ingestion. There have been no reports of harm to the infant. If used, infants should be monitored for bruising.

Efficacy

In the *RE-LY* trial, 18,113 patients with non-valvular AF and intermediate risk for thromboembolism (mean $CHADS_2$ score of 2.1) were randomly assigned to receive oral dabigatran at one of two doses (110 or 150 mg) bd or warfarin. Dabigatran 110 mg met the criteria for non-inferiority, compared with warfarin (RR 0.90, 95% CI 0.74–1.10), while dabigatran 150 mg was significantly more effective than warfarin (RR 0.65, 95% CI 0.52–0.81). The risk of major bleeding was significantly less with dabigatran 110 mg than warfarin (RR 0.80, 95% CI 0.69–0.93, $p = 0.003$), and dabigatran 150 mg had equivalent risk of major bleeding compared to warfarin (RR = 0.93, 95% CI 0.81–1.07, $p = 0.31$). There was an increased risk of gastrointestinal bleeding for 150 mg dabigatran compared to warfarin (RR = 1.50, 95% CI 1.19–1.89, $p < 0.001$); no similar relationship was seen at the lower dose. The risk of minor bleeding, and intracranial bleeding were lower at both dabigatran doses compared to warfarin.

Dosing and monitoring

Dosing

The recommended daily dose for prevention of stroke in non-valvular AF is 220–300 mg taken as one 110 or 150 mg capsule bd (reduce dose in the elderly, see above). In patients with renal impairment a dose of 150 mg administered as one 75 mg capsule bd is recommended. There is discrepancy on the threshold for dose reduction between the UK and US recommendations. The UK recommendations state that a CrCl of 30–50 mL/min should prompt a dose reduction. Whereas in the US it is recommended that dose reduction take place if CrCl is between 15 and 30 mL/min. For each respective recommendation, therapy is not indicated below the lowest range (<30 mL/min UK, <15 mL/min US).

Monitoring

Dabigatran does not currently require routine anticoagulant monitoring. However, recently released analyses from the RE-LY trial suggest that a one-off or annual measurement of dabigatran plasma levels may reduce the rate of bleeding by 30–40%, without affecting the chances of ischaemic stroke. Whether this becomes routine in the future is as yet unclear. The INR test is unreliable and therefore should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT), and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardized, and results should be interpreted with caution. Monitor renal function at least annually, more frequently in the elderly.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability of dabigatran is ~6.5%. T_{max} is 0.5–2 h. Food co-ingestion delays T_{max} but has no effect on bioavailability. After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran by esterase-catalysed hydrolysis. Dabigatran undergoes minimal metabolism to acyl glucuronides, which retain pharmacological activity. Eighty-five per cent of dabigatran is eliminated in the urine.

Interactions

See Table 24.16.

Table 24.16 Interactions of dabigatran

Medications which alter dabigatran plasma levels	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenytoin, rifampicin, and St John's wort Levels increased: amiodarone, ciclosporin, dronedrone, ketoconazole, itraconazole, rilpivirine, tacrolimus, telaprevir, and verapamil	With antiplatelets, anticoagulants, NSAIDs, and SSRIs: increased risk of bleeding

References

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Dantrolene

Dantrolene is a skeletal muscle relaxant, first used as a treatment for spasticity in the 1970s. It is now much better known for its use in the treatment of malignant hyperthermia and is generally reserved as a second-line agent in spasticity.

Uses

Licensed uses

In the UK

- *Spasticity*: dantrolene is licensed for the treatment of chronic, severe spasticity in individuals aged 18 years and older.
- *Malignant hyperthermia*: the IV preparation is licensed for the treatment of malignant hyperthermia in individuals aged 18 years and older.

In the USA

- *Spasticity*: dantrolene is licensed for the treatment of chronic spasticity of UMN origin in individuals aged 5 years and older.
- *Malignant hyperthermia*: the IV formulation is licensed for the treatment of malignant hyperthermia in individuals of all ages. PO and IV formulations are also licensed for preoperative/postoperative prevention of malignant hyperthermia in individuals of all ages (IV) and individuals aged 5 years and older (PO).

Off-label uses

- Treatment of NMS and serotonin syndrome.

Presentation

- *Trade names*: Dantrium®, Dantrium® IV, Revonto, and Ryanodex. Generics are not available.
- *Formulations*: dantrolene is available as a capsule and powder for reconstitution as an IV infusion. Capsule: 25 mg and 100 mg. Powder: 20 mg and 250 mg.

Mechanism of action

Dantrolene acts at the level of muscle fibres by blocking the RyR1 channel, through which calcium is released from the sarcoplasmic reticulum. With regards to spasticity, the reduction of free calcium reduces actin–myosin cross-linkage, and thus excitation–contraction coupling. This results in muscle relaxation. Regarding malignant hyperthermia syndrome, it is thought that dantrolene normalizes the pathologically elevated ionized calcium levels in the myoplasm.

Toxicity and side effects

- *Common—Cardiovascular*: exacerbation of heart failure, hyper-/hypotension, and tachycardia. *Dermatological*: hyperhidrosis, rash. *Gastrointestinal*: abdominal pain, anorexia, constipation, diarrhoea, dysphagia, nausea, vomiting. *Neurological*: dizziness, drowsiness, fever, headache, seizures, speech disturbance. *Ophthalmological*: visual disturbance. *Psychiatric*: confusion, depression, insomnia. *Respiratory*: dyspnoea, pleural effusion, respiratory depression. *Urological*: crystalluria, frequency, haematuria, incontinence, retention.

- *Severe—Cardiovascular*: pericarditis has been reported. *Gastrointestinal*: fatal hepatotoxicity has been reported in clinical trials. This is commoner with females, those over 35, those with a previous history of hepatic dysfunction, those on long-term high-dose therapy, and those concurrently using alternative hepatotoxic agents, including tizanidine (co-prescription should be avoided). *Haematological*: aplastic anaemia, neutropenia, and thrombocytopenia have been reported.

Contraindications

- *Absolute*: hypersensitivity to dantrolene, hepatic dysfunction (except for emergencies in the setting of malignant hyperthermia), and acute muscle spasm.
- *Relative*: concomitant calcium channel blockers (potential for profound hyperkalaemia and ventricular fibrillation).

No dosage adjustment is required in renal impairment.

Use in special populations

- *Elderly*: the elderly may be more susceptible to hepatotoxicity and sedation. Cautious dose titration is recommended.
- *Pregnancy*: embryo toxicity has been observed in animal studies, and thus use in pregnancy is not recommended. It should only be given during pregnancy if the potential benefit outweighs the risk to the fetus.
- *Lactation*: dantrolene is excreted into breast milk in potentially significant quantities, so either dantrolene or breastfeeding should be discontinued.

Efficacy

A 2004 systematic review found dantrolene to be superior to placebo for relieving spasticity of various aetiologies in 7 out of 16 small trials, although outcomes measured varied widely. The only available head-to-head data come from three small trials comparing dantrolene to diazepam, in which no difference in efficacy was found. The limited evidence available suggests overall tolerability is broadly comparable to baclofen and tizanidine. With regards to efficacy in treatment of malignant hyperthermia, a 1984 multicentre study demonstrated no mortalities in 11 cases of malignant hyperthermia when treated with dantrolene. This was thought to be an improvement over the predicted mortality for malignant hyperthermia. Since the introduction of dantrolene, there has been a substantial decrease in the fatality rate of malignant hyperthermia from 70–80% in the 1970s to near 5% now. This reduction is thought to be, in part, due to the introduction of dantrolene.

Dosing and monitoring

Dosing

- *Malignant hyperthermia*: administer a rapid IV dose at 1 mg/kg; this can be increased until symptoms subside, or 10 mg/kg has been given. Oral dantrolene can be given at 4–8 mg/kg/day in four divided doses for 1–3 days post-crisis to prevent recurrence.
- *Spasticity*: start treatment at 25 mg od; after 1 week, increase to 25 mg bd, an extra 25 mg added to each dose or an extra dosing interval is

then added in alternate weeks up to a maximum of 400 mg daily in four divided doses. If no increased benefit is seen after dose escalation, the dose should be stepped down to the previous efficacious dose. If no benefit is seen at the highest dose, therapy should be discontinued after 6–8 weeks.

Monitoring

LFTs should be performed at baseline and repeated regularly during the first year. Patients and carers should be educated regarding the signs of early hepatic dysfunction (pruritus, pale stools, dark urine, nausea, vomiting, etc.)

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 70%. Peak plasma levels occur at 3–6 h. Plasma half-life is 6–9 h, with plasma concentrations remaining therapeutic for ~5 h. There is no significant effect of food on absorption or metabolism. Dantrolene is a CYP3A4 substrate (though not an inducer or inhibitor) and mainly undergoes hydroxylation in the liver to 5-hydroxydantrolene, which has similar efficacy and a longer half-life, compared to the parent compound. Elimination is predominantly renal, primarily as 5-hydroxydantrolene. A small percentage is excreted as unchanged dantrolene.

Interactions

See Table 24.17.

Table 24.17 Interactions of dantrolene

Medications which alter dantrolene plasma levels	Pharmacodynamic interactions
Levels decreased: CYP3A4 inducers, e.g. rifampicin. Levels increased: CYP3A4 inhibitors, e.g. ketoconazole	With calcium channel blockers (non-dihydropyridine): hyperkalaemia, reduced cardiac output (avoid combination) With CNS depressants: increased sedation With hepatotoxic agents, e.g. tizanidine: increased risk of hepatotoxicity With vecuronium: increased risk of neuromuscular block

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Desmopressin

Desmopressin was first used in the treatment of diabetes insipidus in the 1970s. Today, it is most commonly used in the management of cranial diabetes insipidus, haemophilia, and primary enuresis in children. It can also be used as a second-line therapy in the management of nocturia in patients with MS. Although used in small doses for the latter indication, its use is limited by the potential to develop symptomatic hyponatraemia, and, for this reason, it should be avoided in patients with fluid overload syndromes, e.g. heart failure.

Uses

Licensed uses

In the UK

Desmopressin intranasal solution is licensed for the treatment of nocturia associated with MS where other treatments have failed in individuals aged up to 65 years of age.

In the USA

Desmopressin is licensed for the treatment of nocturia resulting from nocturnal polyuria.

Off-label uses

- None.

Presentation

Only the intranasal solution is licensed for use in the management of nocturnal enuresis associated with MS in the UK, although other formulations, most commonly tablets, are used off-label for this indication. Solutions for IV injections are used for other indications. Only the nasal and tablet forms are discussed further below.

- *Trade names*: DDAVP®, DDAVP Rhinal tube®, DesmoMelt®, Desmotabs®, Desmospray®, Nocdurna®, Noctiva®, and Noqdirna®. Generics are available.
- *Formulations*: desmopressin is available as a nasal solution, a nasal spray, a standard tablet, and a sublingual tablet. Nasal solution: 2.5 mL and 5 mL vials at 0.01%. Nasal spray: 0.86, 1.66, or 10 micrograms/metered spray. Standard tablet: 100 micrograms and 200 micrograms. Sublingual tablet: 25 micrograms, 50 micrograms, 60 micrograms, 120 micrograms, and 240 micrograms.

Mechanism of action

Desmopressin is a structural analogue of vasopressin (ADH), a nanopeptide produced by the pituitary gland with vasopressor and antidiuretic effects. Its molecular structure differs slightly from vasopressin, meaning that there is a loss of affinity for vasopressin type 1 receptors (V1) and a relative increase in affinity for V2 receptors. V1 receptors are predominantly responsible for vasopressor activity, and V2 receptors are responsible for antidiuretic activity. Therefore, desmopressin has 12 times greater antidiuretic activity, and 200 times less vasopressor activity, than endogenous vasopressin. The antidiuretic effect of desmopressin through the V1 receptor is mediated by increased permeability of the renal collecting ducts, thereby increasing reabsorption of water.

Toxicity and side effects

- *Common—Cardiovascular*: fluid retention. *Gastrointestinal*: abdominal pain, nausea, and vomiting. *Neurology*: headache.
- *Serious—Dermatological*: severe allergic reactions. *Endocrine*: hyponatraemia, which can be severe and result in convulsions.

Contraindications

- *Absolute*: Patients with increased risk of hyponatraemia, including heart failure and other fluid overload syndromes requiring diuretics, psychogenic polydipsia, and polydipsia associated with alcohol dependence.
- *Relative*: use with caution in patients with cardiovascular disease, cystic fibrosis, hypertension, and hyponatraemia and those at risk of raised intracranial pressure (ICP), and avoid for nocturnal enuresis in the elderly (>65 years of age). Use with caution in patients with renal failure, and avoid if CrCl is <50 mL/min. No precautions or dose adjustments are routinely recommended in hepatic impairment.

Use in special populations

- *Elderly*: avoid in individuals aged >65 years, if possible, due to age-related increase in the risk of cardiovascular and renal disease. If used in older patients, more frequent monitoring of sodium levels is advised.
- *Pregnancy*: animal studies and one low-quality epidemiological study of desmopressin use in pregnant women with diabetes insipidus have not shown an increased risk of teratogenicity with use of the drug; however, a few case studies have documented congenital anomalies in patients on desmopressin therapy. There may be an increased risk of pre-eclampsia; hence the manufacturer advises to avoid use, where possible.
- *Lactation*: desmopressin is present in negligible quantities in breast milk following intranasal spray and is poorly absorbed orally. There is no data on the use of the sublingual or standard tablet and hence these should be avoided or used with caution in nursing mothers.

Efficacy

Three small RCTs have investigated the use of desmopressin in the management of nocturia in patients with MS. All three trials demonstrated a significant reduction in the frequency of voiding and improved sleep, although there was no significant reduction in episodes of incontinence. In the oldest trial, nocturia was reduced from an average of 2.55 voids per night to 1.28 with desmopressin vs. 2.01 with placebo ($p < 0.01$), and, in the most recent trial, the maximum hours of uninterrupted sleep increased from 3.74 to 5.77 with desmopressin treatment. Reports compiled by the Medicines and Healthcare Products Regulatory Agency (MHRA) in 2007 suggested that the nasal spray may be associated with a higher rate of hyponatraemia than the oral formulations, and hence many prescribers will opt to first try oral desmopressin. Newer low-dose nasal formulations (0.86 and 1.66 microgram per metered spray) have demonstrated lower rates of hyponatraemia in general for patients with nocturnal polyuria; however, no studies have specifically validated the improved side effect profile in a MS specific population.

Dosing and monitoring

Dosing

Nasal solution: 0.86–20 micrograms. Standard tablet: 100–200 micrograms. Sublingual tablet: 25–120 micrograms. The dose should be taken at bedtime, and fluid intake should be limited to a minimum from 1 h before to 8 h after dosing. Do not repeat dosing within 24 h. Women are more sensitive to the effects of desmopressin therefore a lower dose may be indicated for the desired effect.

Monitoring

Sodium should be measured before, within 1 week of starting, and approximately 1 month after starting therapy. Hyponatraemia should prompt cessation of therapy.

Pharmacokinetics and interactions

Pharmacokinetics

The average bioavailability and T_{max} of intranasal, oral, and sublingual routes are ~10% and 1 h, 0.08–0.16% and 1.5–2 h, and 0.25% and 0.5–2 h, respectively, although this is highly variable between patients. The route of metabolism is not clear, although *in vitro* experiments suggest it is unlikely to be hepatic. The half-life for all routes is ~3 h. Elimination is predominantly renal.

Interactions

See Table 24.18.

Table 24.18 Interactions of desmopressin

Medications which alter plasma levels of desmopressin	Pharmacodynamic interactions
Levels increased: loperamide	With NSAIDs, TCAs, SSRIs, chlorpromazine, opioid analgesics, carbamazepine, lamotrigine, thiazide diuretics, and chlorpropamide: may increase the risk of fluid retention and hyponatraemia. With conivaptan, demeclocycline, and lithium: may reduce the effect of desmopressin

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Dexamfetamine (dexamphetamine) sulfate

Dexamfetamine was first marketed in the UK in the 1930s. It is a centrally acting stimulant drug used as a second-line agent in the treatment of narcolepsy if modafinil is not effective. Older studies have demonstrated its effectiveness at promoting wakefulness, although its behavioural and cardiovascular side effects, in addition to its potential as a drug of abuse, limit its wider use.

Uses

Licensed uses

In the UK/USA (licensing is the same)

- Narcolepsy: Dexamfetamine is licensed for use in the treatment of narcolepsy in individuals aged 3 years and older.

Off-label uses

- None.

Presentation

- *Trade names*: Amfexa®, Dexedrine®, Dextrostat®, Liquadd®, and ProCentra®. Generics are available.
- *Formulations*: dexamfetamine is available as an oral solution, standard tablets, and sustained-release capsules. Oral solution: 5 mg/5 mL. Standard tablets: 5 mg and 10 mg. Sustained-release capsules: 5 mg, 10 mg, and 15 mg.

Mechanism of action

Dexamfetamine sulfate is a non-catecholamine, sympathomimetic amine which acts as a central stimulant by promoting the release of catecholamines and, to a lesser extent, by preventing their reuptake into presynaptic nerve terminals by competitive inhibition.

Toxicity and side effects

- *Common—Gastrointestinal*: abdominal pain, anorexia, nausea, unpleasant taste, vomiting, and weight loss. *Neurological*: fatigue and insomnia. *Psychiatric*: anxiety, behavioural disturbance, e.g. aggression and elation.
- *Serious—Cardiovascular*: cardiomyopathy and MI can occur. *Gastrointestinal*: ischaemic colitis. *Musculoskeletal*: rhabdomyolysis. *Neurological*: cerebral vasculitis, NMS, movement disorders, including tics, seizures, and stroke. *Ophthalmological*: rarely angle-closure glaucoma. *Psychiatric*: delirium, panic states, psychosis.
- *Withdrawal* –Cessation or reduction in amphetamine use can result in withdrawal symptoms, including anhedonia, fatigue, insomnia/hypersomnia, or psychomotor agitation or retardation.

Contraindications

- *Absolute*: hypersensitivity to dexamfetamine or its excipients. Patients with advanced atherosclerosis, symptomatic cardiovascular disease, cardiomyopathy, or moderate-to-severe hypertension. Patients with

Gilles de la Tourette syndrome or other tic disorders, glaucoma, hyperthyroidism, or porphyria. Patients with anorexic disorders, psychotic symptoms, schizophrenia, severe depression, or suicidal ideation. Dexamfetamine is also a potential drug of abuse and should be avoided in patients with a history of alcohol or drug abuse. It should also be avoided during, or for 14 days after, treatment with an MAOI. Tablets contain lactose and sucrose, and hence patients with hereditary problems of lactose/sucrose metabolism should avoid dexamfetamine.
- *Relative*: use with caution in patients on guanethidine, and those with mild hypertension, family history of tic disorders, renal impairment, or unstable personalities. Dexamfetamine lowers the seizure threshold; hence use with caution in epilepsy. Dexamfetamine causes weight loss; hence use with caution in anorexia nervosa. No alteration in dose is given in the product literature with regard to hepatic impairment; however, dexamfetamine is extensively hepatically metabolized and hence should be used with caution in patients with hepatic dysfunction.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and have a higher risk of dexamfetamine exacerbating pre-existing cardiovascular and cerebrovascular disorders. Hence half of the adult dose should be used in those >65 years of age.
- *Pregnancy*: evidence is based on illicit exposure and animal studies. There is limited data from use of dexamfetamine in pregnant women: one study has suggested an increased risk of pre-eclampsia and preterm birth. Use in pregnancy is contraindicated, as it may lead to increased risk of premature death, low birthweight, neonatal withdrawal syndromes, and potentially behavioural disorders in childhood.
- *Lactation*: the exact amount of dexamfetamine present in human breast milk is unknown. Dexamfetamine may reduce breast milk production, and transmission to a nursing infant may be associated with behavioural disturbance. Mothers using dexamfetamine should use alternative feeding methods where possible.

Efficacy

There is little high-quality evidence looking at the effects of dexamfetamine in the management of narcolepsy. Older studies investigated the effects of medications on multiple sleep latency testing (i.e. how fast one falls asleep in a quiet environment—as a measure of excessive daytime sleepiness). One survey demonstrated that use of dexamfetamine resulted in a significant increase in sleep latency from 35% to 70% of normal ($p = 0.01$).

Dosing and monitoring

Dosing

For the treatment of narcolepsy, age >12 years: start treatment at 10 mg in divided doses (first dose on waking and further doses at 4–6 h intervals). This can be increased by 10 mg at weekly intervals, depending on side effects, up to a maximum of 60 mg.

Monitoring

Assess the BP and cardiovascular risk and consider an ECG at baseline. Then monitor the BP and cardiovascular risk profile on a regular basis, while on treatment. Monitor psychiatric status, especially for exacerbations of previous psychiatric illness, every 6 months.

Pharmacokinetics and interactions

Pharmacokinetics

Knowledge of the pharmacokinetics of dexamfetamine is limited. The oral bioavailability of dexamfetamine is >75%. Peak plasma concentrations are reached at different time points, depending on the formulations used: standard tablets at ~2 h and sustained-release tablets at ~8 h. Thirty to 45% is metabolized hepatically, while the rest is excreted unchanged by the kidneys. The half-life in adults is 10–13 h, although this can be enhanced with acidic urine.

Interactions

See Table 24.19.

Table 24.19 Interactions of dexamfetamine

Medications which alter dexamfetamine plasma levels	Medications whose plasma levels are altered by dexamfetamine	Pharmacodynamic interactions
Levels decreased: gastrointestinal acidifying agents (e.g. fruit juices) and urinary acidifying agents (e.g. ammonium chloride) Levels increased: gastrointestinal alkalizing agents (e.g. sodium bicarbonate) and urinary alkalizing agents (e.g. acetazolamide, some thiazides)	Levels decreased: ethosuximide, phenobarbital, and phenytoin. Levels increased: corticosteroids	With adrenergic blockers and antihypertensives: effects inhibited by dexamfetamine. With catecholamines, MAOIs, and TCAs: increased cardiovascular side effects With lithium and typical antipsychotics: inhibition of central stimulatory effects of amphetamines

References

Mitler MM, Hajdukovic RM. Relative efficacy of drugs for the treatment of sleepiness in narcolepsy. *Sleep* 1991;14(3):218–20.

Mitler MM, Hajdukovic RM, Erman M, Koziol JA. Narcolepsy. *J Clin Neurophysiol* 1990;7(1):93–118.

Morgenthaler TI, Kapur VK, Brown T, *et al*; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;30(12):1705–11.

Diclofenamide

Diclofenamide was approved for use in 1958 in the treatment of glaucoma. From a neurological perspective, it is used as a prophylactic treatment for hyperkalaemic and hypokalaemic periodic paralysis.

Uses

Licensed uses

In the UK/USA

- There are no licensed neurological uses.

Off-label uses

- Prophylaxis of attacks in hyper-/hypokalaemic periodic paralyses.

Presentation

- *Trade name*: Keveyis®. Generics are available.
- *Formulation*: diclofenamide is available as a 50 mg tablet.

Mechanism of action

Diclofenamide is a carbonic anhydrase inhibitor with pharmacological properties similar to those of acetazolamide. The mechanism of action of this class of medications in the periodic paralyses is unclear, but animal studies have shown that, independent of its inhibition of carbonic anhydrase, diclofenamide can open calcium-activated potassium channels to relieve weakness.

Toxicity and side effects

- *Common—dermatological*: pruritus, skin rash. *Gastrointestinal*: anorexia, diarrhoea, nausea, and vomiting. *Metabolic:* hypokalaemia. *Neurological*: drowsiness, paraesthesiae.

Contraindications

- *Absolute*: adrenocortical insufficiency, hepatic insufficiency, renal failure, hyperchloremic acidosis, severe obstructive airways disease.

Use in special populations

- *Elderly*: diclofenamide should be used with caution, as age-related renal impairment increases the risk of metabolic acidosis.
- *Pregnancy*: diclofenamide has been shown to be teratogenic at high doses in animal models; there are no safety data in human studies. It should be avoided in pregnancy, unless potential benefits outweigh risks.
- *Lactation*: it is not known whether diclofenamide is excreted into human breast milk; the manufacturer advises caution in breastfeeding mothers.

Efficacy

Diclofenamide is effective for the prevention of episodic attacks in periodic paralysis, significantly reducing the frequency and severity of attacks in a combined cohort of hypokalaemic periodic paralysis and hyperkalaemic periodic paralysis by a mean of −1.4 attacks/week (95% CI −2.97 to 0.17) and −3.5 attacks/week (−6.38 to −0.62), respectively. There is insufficient evidence to inform whether acetazolamide or diclofenamide is more efficacious for this indication. No established guidelines currently exist for the prophylaxis of attacks of periodic paralysis and whether treatment with carbonic anhydrase inhibitors reduces the risk of developing permanent myopathy later in the natural history of the disease.

Dosing and monitoring

Dosing

Start and continue treatment at 50 mg BD.

Monitoring

A subgroup of patients may suffer from increased periodic paralysis attack frequency with diclofenamide; therefore, regular clinical review is recommended.

Pharmacokinetics and interactions

Pharmacokinetics

The pharmacokinetics of diclofenamide are poorly described. Expert opinion suggests they are similar to those of acetazolamide (see Acetazolamide, p. 500).

Interactions

See Table 24.20.

References

Sansone V, Meola G, Links TP, *et al*. Treatment for periodic paralysis. *Cochrane Database Syst Rev* 2008;1:CD005045.

Table 24.20 Interactions of diclofenamide

Pharmacodynamic interactions
With phenobarbital or phenytoin: increased risk of osteomalacia
With furosemide and steroids: increased likelihood of diclofenamide side effects
With high-dose aspirin (>300 mg/day): risk of anorexia, coma, lethargy, and tachypnoea

Dipyridamole (modified release)

Dipyridamole is an antiplatelet drug with additional activity as a non-nitrate coronary artery vasodilator. It was first used in clinical practice in the 1980s. It is now a second-line drug in the management of ischaemic stroke and TIA.

Uses

Licensed uses

In the UK/USA (licensing is the same)

- *Prevention of stroke*: modified-release dipyridamole is licensed for the secondary prevention of ischaemic stroke and TIAs in individuals aged 16 years and older.

Off-label uses

- Acute stroke and TIA where aspirin and clopidogrel are not tolerated.

Presentation

Dipyridamole MR is available both alone and in combination with low-dose aspirin (25 mg).

- *Trade names*: Aggrenox®, Asasantin Retard® (in combination with aspirin) and Persantin Retard®. Generics of the modified-release form are not available.
- *Formulations*: Asasantin Retard® is available as a 225 mg capsule. Persantin Retard® is available as a 200 mg capsule.

Mechanism of action

Dipyridamole has dual action as both an adenosine uptake inhibitor and a phosphodiesterase inhibitor; by prevention of uptake of adenosine by red blood cells, platelets, and endothelial cells, it increases extracellular adenosine, which both inhibits platelet activation and promotes arteriodilatation via the P1 receptor. Its activity as a phosphodiesterase inhibitor results in an additional vasodilatory effect. Dipyridamole may also stimulate the synthesis and release of prostacyclin.

Toxicity and side effects

- *Common—cardiovascular*: hot flushes, hypotension, tachycardia, and worsening symptoms of coronary artery disease. *Gastrointestinal*: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting. *Neurological*: dizziness, headache, migraine, and risk of exacerbation of weakness in MG.
- *Serious—cardiovascular*: ventricular arrhythmia and MI. *Gastrointestinal*: gastrointestinal bleeding. *Respiratory*: bronchospasm.

Contraindications

(If using Asasantin Retard®, see Aspirin, p. 516)

- *Absolute*: hypersensitivity to the product.
- *Relative*: use with caution in patients with severe coronary artery disease, left ventricular outflow obstruction, or hemodynamic instability (e.g. decompensated heart failure). No dosing adjustments are required in renal impairment or hepatic impairment, unless there are clinical signs of liver failure, in which case dipyridamole should be avoided, as there is no evidence for this patient group. Some formulations contain lactose and sucrose; patients with such intolerances should avoid taking this medication.

Use in special populations

- *Elderly*: plasma concentrations are 30% higher in this population; hence use with caution, as this population may be at increased risk of bleeding and myocardial ischaemia.
- *Pregnancy*: no adverse effects have been identified from animal studies. There are no controlled studies in humans, but it has been used for many years without obvious ill effects. The manufacturer recommends that dipyridamole should be avoided, particularly in the first trimester.
- *Lactation*: Dipyridamole is excreted at levels ~6% of the plasma concentration in breast milk; hence dipyridamole should be avoided in nursing mothers.

Efficacy

The ESPS-2 trial randomly assigned 6602 patients with a recent TIA or ischaemic stroke into either *dipyridamole* monotherapy, *aspirin* monotherapy, a combination of aspirin plus extended-release dipyridamole given bd, or placebo. An independent and significant benefit for stroke risk reduction was observed for both extended-release dipyridamole monotherapy and aspirin monotherapy, compared with placebo ($p <$or $= -0.001$). The benefit of the combination *aspirin with extended-release dipyridamole* was significantly greater still than the two components alone. This effect was confirmed in the ESPRIT trial where the composite primary outcome (death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complications) was significantly less frequent in the aspirin plus dipyridamole group than the aspirin alone group after 3.5 years (13% vs. 16%) (hazard ratio 0.80, 95% CI 0.66–0.98; absolute risk reduction 1.0% per year, 95% CI 0.1–1.8). The PRoFESS trial showed that *clopidogrel* monotherapy and *aspirin with extended-release dipyridamole* have similar risks and benefits for secondary stroke prevention (8.8% vs. 9.0%).

Dosing and monitoring

Dosing

For the secondary prevention of ischaemic stroke and TIAs: 200 mg bd, preferably with meals.

Monitoring

FBC monitoring should be considered in patients deemed at higher risk of bleeding.

Pharmacokinetics and interactions

Pharmacokinetics

Data given are for dipyridamole MR alone (if giving combination aspirin and dipyridamole therapy, see Aspirin, p. 516). Bioavailability is ~70%, due to first-pass metabolism. Peak plasma concentrations occur at 2–3 h after administration. Food co-ingestion has no effect on bioavailability or T_{max}. ~98% of dipyridamole is protein-bound. A steady state occurs at 2 days. Metabolism is predominantly hepatic by conjugation with glucuronic acid to form pharmacologically inactive metabolites: a monoglucuronide and small amounts of a diglucuronide. 95% of these metabolites are excreted into bile. The half-life for conversion of dipyridamole to its metabolites is 2–3 h. The elimination half-life for the metabolites is ~15 h.

Interactions
See Table 24.21.

Table 24.21 Interactions of dipyridamole

Medications which alter dipyridamole plasma levels	Pharmacodynamic interactions
Levels decreased: antacids	Adenosine: dipyridamole enhances and extends the effects of adenosine Antiplatelets, coumarins, NSAIDs, and phenindione: increased risk of bleeding Fludarabine: dipyridamole may reduce effects of fludarabine

References

Diener HC, Cunha L, Forbes C, *et al*. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143(1–2):1–13.

ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;367(9523):1665–1673.

Sacco RL, Diener HC, Yusuf S, *et al*. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *NEJM* 2008;359(12):1238–51.

Efgartigimod alfa

The FDA first approved efgartigimod alfa in 2021. In the UK, it is currently available under an Early Access to Medicines Scheme (as of 2023). It is a first-in-class Fc receptor antagonist, approved for the treatment of generalized myasthenia gravis. It is an effective treatment, without the metabolic side effect profile of corticosteroids. Its use in other autoimmune diseases is under investigation.

Uses

Licensed uses

In the UK/USA

- *Myasthenia gravis:* Efgartigmoid alfa is licensed for the treatment of AChR antibody-positive generalized myasthenia gravis, aged 18 years and older. In the UK, use is restricted to refractory patients where other licensed treatments have wither not been effective or not tolerated.

Off-label uses

- Autoimmune myositis and chronic inflammatory demyelinating polyradiculoneuropathy.

Presentation

- *Trade names*: Vyvgart ®. Generics are not available.
- *Formulations*: Efgartigimod alfa is available as a vial for intravenous infusion. Vial: 20 mL at 20 mg/mL, containing a total of 400 mg.

Mechanism of action

IgG antibodies targeting acetylcholine receptors are the underlying cause for myasthenia gravis. The neonatal Fc receptor binds IgG, prolonging its lifespan by preventing its destruction. Efgartigimod alfa is an IgG1 fragment, which binds and blocks the action of the neonatal FcRn receptor, thereby accelerating the removal of pathogenic antibodies and improving the symptoms of myasthenia gravis.

Toxicity and side effects

- *Common—Dermatological:* rash. *Haematological:* leucopenia. *Infectious*: respiratory and urinary tract infections. *Neurological*: headache, myalgia, and paraesthesia.
- *Serious— Immunological:* Hypersensitivity reactions including angioedema.

Contraindications

- *Absolute*: Hypersensitivity to efgartigimod alfa or any of its excipients.
- *Relative*: Mild renal impairment showed reduced clearance of efgartigimod alfa, but this did not influence the safety profile. Efgartigimod alfa has not been studied in moderate or severe renal impairment. Careful monitoring should be considered if used in these patient groups. No dose adjustment is required if the patient has hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustment is required. Use with caution, as the elderly are more prone to side effects and have an age-related impairment in renal function.
- *Pregnancy*: There is no human data. Animal studies have not demonstrated teratogenic effects. Efgartigimod alfa is likely to be transferred over the placenta to the fetus. Efgartigimod alfa is likely to reduce circulating maternal IgG, meaning that there may be a reduction in passive protection of the newborn. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: Efgartigimod alfa is likely to be present in breastmilk. If used, infants should be monitored for potential side effects such as hypersensitivity reactions and infections. The infant could be switched to an alternative feeding regimen if these are identified.

Efficacy

ADAPT was a phase 3, randomized, placebo-controlled trial of efgartigimod alfa in patients with AChR antibody-positive generalized myasthenia gravis. Patients had to have myasthenia gravis activities of daily living score of at least five, and they had to be on stable doses of at least one other therapy for myasthenia gravis (including corticosteroids and acetylcholinesterase inhibitors). 68% of patients responded to efgartigimod alfa compared to 30% of patients who received placebo ($P<0.0001$) after 8 weeks.

Dosing and monitoring

Dosing

Treatment consists of 10 mg/kg (maximum recommended dose is 1200 mg) of efgartigimod alfa administered by intravenous infusion, over 1 h once weekly for 4 weeks. Maximum recommended dose is 1200 mg per infusion. Typically, at least 50 days should elapse prior to initiating a further treatment cycle.

Monitoring

No specific monitoring protocol is recommended.

Pharmacokinetics and interactions

Pharmacokinetics

Efgartigimod experiences linear pharmacokinetics and exposure increases proportionately after doses up to 50 mg/kg. It is degraded into inactive small peptides and amino acids. The terminal half-life is 3–5 days.

Interactions

Efgartigimod alfa does not have any significant pharmacokinetic interactions.

References

Heo Y. Efgartigmod: first approval. *Drugs* 2022;82(3):341–8.

Howard J, Bril V,Vu T, *et al*. Safety, efficacy, and tolerability of efgartigmod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2021;20(7):526–36.

Fampridine (4-aminopyridine)

Fampridine, or dalfampridine, is a voltage-gated potassium channel blocker that is used for symptomatic treatment in MS. It can also be used off-label for the management of nystagmus and episodic ataxia.

Uses

Licensed uses

In the UK/USA

- *MS*: fampridine is approved to increase walking speed in all forms of MS in patients aged 18 years and older. In the UK, this requires patients to have an EDSS of 4–7.

Off-label uses

- Downbeat nystagmus and episodic ataxia type 2.

Presentation

- *Trade names*: Ampyra® and Fampyra®. Generics are not available.
- *Formulation*: modified-release oral tablet: 10 mg.

Mechanism of action

Fampridine prolongs presynaptic cell membrane depolarization by blockade of presynaptic voltage-gated potassium channels. This reduces the leakage of K+ ionic current and increases the influx of calcium into nerve endings and facilitates exocytosis of acetylcholine-containing vesicles, thereby increasing the speed of action potential conduction. This is thought to increase walking speed in MS, while, in DBN, this mechanism is thought to increase the activity of Purkinje cells in the cerebellum, thereby increasing their inhibitory control of deep cerebellar and vestibular nuclei and ultimately reducing oscillopsia.

Toxicity and side effects

- *Common—Cardiovascular:* palpitations, tachycardia. *Gastrointestinal*: constipation, dyspepsia, nausea, and vomiting. *Genitourinary*: UTI. *Musculoskeletal*: back pain. *Neurological*: dizziness, headache, paraesthesiae, and tremor. *Psychiatric*: anxiety and insomnia. *Respiratory*: nasopharyngitis and pharyngolaryngeal pain.
- *Serious—Immunological*: anaphylaxis. *Neurological*: seizures.

Contraindications

- *Absolute*: hypersensitivity, seizures, renal impairment (CrCl <80 mL/min), and concurrent use of other forms of 4-AP. Fampridine should be administered with caution in the presence of any other factors that may lower seizure threshold.
- *Relative*: no dose adjustment is required in patients with hepatic impairment. Fampridine should be used with caution in patients with arrhythmias or conduction blocks, as there is limited safety data in these patients. Fampridine may also lead to increased dizziness and balance disorders.

Use in special populations

- *Elderly*: this drug has not been studied in the elderly, but renal function should be checked prior to initiation and during treatment in this group.
- *Pregnancy*: animal studies have shown teratogenicity; there is limited data in human studies. This drug should not be used during pregnancy.
- *Lactation*: It is not known if fampridine is excreted in human milk. Breastfeeding should be avoided.

Efficacy

- *EA2*: a double-blind, randomized, placebo-controlled cross-over trial ($n = 10$) of 4-AP (5 mg tds for 2–3 months, with 1-month washout) in EA2 found 4-AP significantly reduced the frequency and duration of attacks (median monthly frequency—4-AP: 1.65, placebo: 6.50 ($p = 0.03$); duration—4-AP: 4.45 h, placebo: 13.65 h ($p = 0.08$)) and improved quality of life, as demonstrated by improved outcomes in the Vestibular Disorders Activities of Daily Living Scale, which showed a decrease from 6.00 to 1.50 ($p = 0.02$) with 4-AP treatment compared to placebo.
- *MS*: a 40% responder rate in a timed 25 ft walk has been shown with fampridine 10 mg bd in placebo-controlled trials of relapsing-remitting and progressive MS. Responders demonstrated a >20% increase in speed of timed walk.

Dosing and monitoring

Dosing

- *Nystagmus*: an observed test dose is often given first where patients are given either the medication or a placebo, and then the degree of nystagmus, gait, and dynamic visual acuity are assessed pre- and post-dosing. If the test dose is successful, then start treatment at 10 mg od, and increase by 10 mg every 1–2 weeks, as required/tolerated, up to 10 mg tds.
- *MS*: start treatment at 10 mg bd. The response to treatment should be assessed using a timed 25 ft walking test that is performed before initiation and after 2–4 weeks. The drug should be discontinued after 2–4 weeks if there is no improvement. If deterioration in walking later develops, then the drug should be withdrawn, and the response to treatment should be reassessed with a further 2-week trial.

Monitoring

Perform an ECG at baseline. Some centres may use cardiac monitoring during the first test dose to assess for the presence of arrhythmia.

Pharmacokinetics and interactions

Pharmacokinetics

The absolute bioavailability is not known, and the relative bioavailability is 96%, compared to the aqueous oral solution. When taken with food, there is a 2–7% reduction in AUC, which does not decrease therapeutic efficacy. However, because C_{max} increases 15–23%, it is recommended that fampridine is not taken with food. Fampridine is a lipid-soluble product and can cross the blood–brain barrier. Fampridine undergoes a minimal amount of hepatic metabolism; CYP2E1 hydroxylates fampridine to 3-hydroxy-4-AP. The terminal elimination half-life is 5.2–6.5 h, and elimination is nearly complete at 24 h; 95.9% is excreted in the urine, and 90.3% of this is unaltered drug.

Interactions

See Table 24.22.

Table 24.22 Interactions of fampridine

Pharmacodynamic interactions
With cimetidine: the manufacturers advise against concomitant use

References

Claassen J, Teufel J, Kalla R, *et al*. Effects of dalfampridine on attacks in patients with episodic ataxia type 2: an observational study. *J Neurol* 2013;260(2):668–9.

Goodman AD, Brown TR, Edwards KR, *et al*.; MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010;68(4):494–502.

Strupp M, Kalla R, Claassen J, *et al*. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurol* 2011;77(3):269–75.

Felbamate

Felbamate was originally developed in the 1950s as a potential anxiolytic. It was only 30 years later that research on stroke patients found that it was effective as an ASM. In the USA, it is strictly a second-line agent. It has been associated with the rare, but severe, side effects of aplastic anaemia and hepatic failure, limiting its wider use in the treatment of epilepsy.

Uses

Licensed uses

In the USA

- *Epilepsy*: felbamate is licensed as monotherapy or as an adjunct for the treatment of focal seizures with or without secondary generalization in adults (14 years of age and older) and for the treatment of focal-onset and generalized seizures associated with LGS in children aged 2–14 years old. It is not licensed as a first-line therapy and should only be used in patients failing to respond to alternative ASMs. Patients should only be prescribed felbamate if they have epilepsy that is so severe that it outweighs the risk of aplastic anaemia and hepatotoxicity.

Felbamate is not licensed for use in the UK.

Off-label uses

- Absence seizures.

Presentation

- *Trade names*: Felbatol®. Generics are not available.
- *Formulations*: Felbamate is available as an oral suspension and as a scored tablet. Oral suspension: 600 mg/5 mL. Tablet: 400 mg and 600 mg.

Mechanism of action

The exact mechanism of action of felbamate has not been fully determined. It has several actions, including: (1) channel-blocking activity via both NMDA and non-NMDA subunits of glutamate receptors; (2) inhibition of voltage-gated sodium channels; (3) barbiturate-like modulation of GABA receptors; (4) inhibition of glutamatergic neurotransmission via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors.

Toxicity and side effects

- *Common—Gastrointestinal*: anorexia, dyspepsia, and nausea, which can result in a temporary weight loss in >50% of patients. *Neurological*: diplopia, dizziness, gait disturbance, headache, insomnia, and irritability.
- *Serious—Gastrointestinal*: fulminant hepatic failure in 1/7000 to 1/22 000, fatal in 50%. *Haematological*: rarely, aplastic anaemia has been described at an estimated incidence of 1/5000 to 1/20 000, with a mortality rate of 40%. The incidence is commoner in individuals who: (1) are over 18 years of age; (2) are female; (3) have a current or previous history of blood dyscrasia; (4) are being treated with multiple

AEDs; and (5) have clinical/serological evidence of an immune disorder. Serious side effects usually occur in the first 6 months of treatment. They are rare after 18 months. *Psychiatric:* suicidality.

Contraindications

- *Absolute*: known hypersensitivity to felbamate, its excipients, or other carbamates; hepatic dysfunction and blood dyscrasia.
- *Relative*: 50% of felbamate is excreted renally; hence lower doses are required in renal impairment.

Use in special populations

- *Elderly*: although no systematic studies in this demographic have been performed, the elderly have an age-related deterioration in their renal and hepatic function, and so they may benefit from lower dosing regimens.
- *Pregnancy*: animal trials have shown some teratogenic effects; there have been no studies of teratogenicity in humans. Use in pregnancy involves weighing up the potential benefits and side effects. There is no available data on the pharmacokinetics of felbamate during pregnancy.
- *Lactation*: felbamate has been detected in breast milk; it is not known at what concentrations. Breastfeeding is not recommended until the safety of felbamate is verified with additional research, especially given its potential to cause severe haematologic and hepatic toxicity.

Efficacy

An RCT compared felbamate with placebo in 73 patients with LGS. Felbamate treated patients demonstrated a 19% drop in their total seizures compared to 4% with placebo $p = 0.01$.

Dosing and monitoring

Dosing

For the treatment of epilepsy, age >12 years: start treatment at 600 mg bd. This can be increased by 600 mg bd on a weekly basis up to 3600 mg/day. In adults, doses of up to 6000 mg/day have been used.

Monitoring

FBC and LFTs should be performed at baseline, 1 month, and then every 3 months that treatment is continued.

Therapeutic drug monitoring Optimum seizure control when used in monotherapy occurs at plasma concentrations of 30–60 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is ~90%. T_{max} occurs at 3–5 h. The half-life is 20–23 h. Less than 25% of felbamate is bound to plasma protein. Fifty per cent of felbamate is metabolized by the liver; 95% of the dose is eliminated by the renal system as metabolites and the unchanged medication.

Interactions

See Table 24.23.

Table 24.23 Interactions of felbamate

Medications which alter felbamate plasma levels	Medications whose plasma levels are altered by felbamate
Levels decreased: carbamazepine, phenobarbital, phenytoin. Levels increased: gabapentin	Levels decreased: carbamazepine, vigabatrin, and warfarin. Levels increased: carbamazepine–epoxide metabolite of carbamazepine, clobazam, clonazepam, lamotrigine, methsuximide, phenobarbital, phenytoin, and valproate (reduce dose of carbamazepine, phenytoin, phenobarbital, and valproate by 20% when initiating felbamate)

References

Felbamate study group in Lennox–Gastaut syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox–Gastaut syndrome). *NEJM* 1993;328(1):29–33.

Fludrocortisone

Fludrocortisone was first used in the 1950s for primary and secondary adrenocortical insufficiency in Addison's disease. It can be used in the management of orthostatic hypotension when conservative measures have failed in PD and other disorders associated with autonomic neuropathy.

Uses

Licensed uses

- Fludrocortisone has no licensed neurological uses.

Off-label uses

- Orthostatic hypotension associated with autonomic neuropathy, MSA, and PD.

Presentation

- *Trade names*: Florinef®. Generics are available.
- *Formulations*: fludrocortisone is available as 100-microgram tablets.

Mechanism of action

Fludrocortisone is a synthetic mineralocorticoid with minimal glucocorticoid effects. It acts on the distal tubule to increase renal sodium reabsorption and expands plasma volume. It also increases excretion of potassium and hydrogen in the urine.

Toxicity and side effects

Corticosteroid side effects are uncommon with fludrocortisone at the doses used to treat postural hypotension (see Corticosteroids, p. 386).

- *Common—Cardiovascular*: fluid retention, hypertension, hypokalaemia, and hypokalaemic alkalosis. *Neurological*: headache when supine.

- *Serious—Cardiovascular*: congestive heart failure in susceptible patients, cardiac arrhythmias, or ECG changes due to potassium deficiency. *Haematological*: thromboembolism.

Contraindications

- *Absolute*: hypersensitivity to fludrocortisone or its excipients, and untreated systemic fungal infection.
- *Relative*: caution should be used with patients with known electrolyte disturbance or fluid overload. For further contraindications of corticosteroids, see Corticosteroids, pp. 304–8. Fludrocortisone should be used with caution in patients with hepatic or renal impairment, although no dose adjustment is routinely recommended.

Use in special populations

- *Elderly*: systemic corticosteroid side effects are more common in the elderly, and closer monitoring is required. No specific dosage recommendations are available.
- *Pregnancy*: the potential of fludrocortisone to cause fetal harm during pregnancy is still somewhat unclear. In animals, fludrocortisone has been shown to have deleterious effects on pregnancy, resulting in cleft palate and intrauterine growth retardation in certain cases. Use only if benefits outweigh risks. Dose alteration is not required. Newborns should be monitored for hypoadrenalism.
- *Lactation*: corticosteroids are found in breast milk. Fludrocortisone should be used with caution in nursing mothers, and the infant monitored for signs of hypoadrenalism.

Efficacy

In PD, the prevalence of orthostatic hypotension may be as high as 60%. However, there is a lack of robust trial evidence for the efficacy of fludrocortisone in PD. Small studies have suggested that it may be safe in this context. One study found that fludrocortisone (0.2 mg/day) was superior to pyridostigmine bromide in the treatment of orthostatic hypertension in PD, resulting in peripheral hypertension but no central supine hypertension. A recent systematic review of 13 studies found equivocal data supporting the influence of fludrocortisone on blood pressure, orthostatic symptoms, and adverse events in PD patients with orthostatic hypotension. Expert consensus suggests that it is an effective treatment option if non-pharmacological therapies have failed.

Dosing and monitoring

Dosing

The typical dose of fludrocortisone is 0.1 mg/day. Dosage can range from 0.05 mg to 0.3 mg/day. Dosage should be decreased by 0.05 mg/day if transient hypertension arises due to therapy.

Monitoring

Monitor blood pressure and serum electrolytes (including potassium) regularly. Dietary salt restriction and potassium supplementation may be required.

Pharmacokinetics and interactions

Pharmacokinetics

Fludrocortisone is rapidly and completely absorbed after oral administration. T_{max} is 4–8 h. It is 70–80% bound to plasma proteins. The plasma half-life is ~3.5 h. ~80% is excreted in the urine; excretion into the bile is balanced by reabsorption in the intestine; and a small amount is excreted in the faeces.

Interactions

See Table 24.24.

Table 24.24 Interactions of fludrocortisone

Medications which alter fludrocortisone plasma levels	Pharmacodynamic interactions
Levels decreased: Barbiturates, phenytoin, and rifampicin.	With Amphotericin B, Digitalis glycosides, potassium-depleting diuretics: can enhance hypokalaemia. With oral anticoagulants: can decrease prothrombin time response. With antidiabetic drugs (oral medications and insulin): can decrease antidiabetic effect. With aspirin: can increase ulcerogenic effect and decrease pharmacologic effect. With anabolic steroids (i.e. C-17 alkylated androgens including oxymetholone, methandrostenolone, and norethandrolone): can enhance tendency toward oedema

Also see Corticosteroids, p. 386.

References

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Gabapentin (including gabapentin enacarbil)

Gabapentin was initially marketed as an antiepileptic in the 1990s. It was deliberately designed to mimic the inhibitory neurotransmitter GABA. In fact, the best evidence suggests it probably works via an alternative mechanism. Due to its narrow spectrum of activity and limited efficacy, it is not commonly used in the management of epilepsy but has found use in the treatment of many other neurological disorders, most commonly neuropathic pain.

Gabapentin enacarbil is a new prodrug of gabapentin which has up to double the oral bioavailability of gabapentin. It is not widely available in Europe and is not licensed in the UK. It is predominantly used in the management of restless legs syndrome (RLS), for which it was approved by the FDA in 2011. The majority of the information with regard to gabapentin enacarbil is similar to that of gabapentin. Variations in the use of the two drugs are highlighted below.

Uses

Gabapentin.

Licensed uses

In the UK/USA

- *Epilepsy*: gabapentin is licensed as a monotherapy for the treatment of focal-onset seizures, with or without secondary generalization, in individuals aged 12 years and older (UK and USA). As an adjunct, it is licensed for the treatment of focal-onset seizures, with or without secondary generalization, in individuals aged 6 years and older in the UK and aged 3 years and older in the USA.
- *Neuropathic pain*: gabapentin is licensed for the treatment of peripheral neuropathic pain in individuals aged 18 years and older. (In the USA, its licence is limited to the treatment of post-herpetic neuralgia.)

Gabapentin enacarbil.

Licensed uses

In the USA

- *Neuropathic pain*: gabapentin enacarbil is licensed for the treatment of post-herpetic neuralgia in individuals aged 18 years and older.
- *RLS*: gabapentin enacarbil is licensed for the treatment of moderate-to-severe RLS in individuals aged 12 years and older.

Off-label uses

- Central neuropathic pain, ET, insomnia, PLMS, prophylaxis of migraine, spasticity (in MS and spinal cord injury/disease), short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), and trigeminal neuralgia. Standard-formulation gabapentin has also been used off-label in the management of RLS.

Presentation

1. Gabapentin.

- *Trade names*: Gralise® and Neurontin®. Generics are available.
- *Formulations*: gabapentin is available as a capsule, an oral solution, and a tablet. Capsule: 100 mg, 300 mg, and 400 mg. Oral solution: 50 mg/mL. Tablet: 600 mg and 800 mg.

2. Gabapentin enacarbil.

- *Trade names*: Horizant®. Generics are not available.
- *Formulations*: gabapentin enacarbil is available as extended-release tablets in 300 mg and 600 mg doses.

Mechanism of action

The exact mechanism of action of gabapentin has not been fully determined. *In vitro* studies have shown it binds to the $\alpha 2\delta$ subunit of VGCCs. This binding closes presynaptic calcium channels and suppresses neuronal activity; this presumably inhibits the activity of nociceptive neurons, as well as pathways involved in the generation of epileptic activity, movement disorders, and spasticity. Gabapentin enacarbil is the prodrug of gabapentin, which is believed to be responsible for most of its therapeutic action.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension, peripheral oedema, and vasodilation. *Dermatological*: acne, facial oedema, rash, purpura, and pruritus. *Gastrointestinal*: abdominal pain, bowel disturbances, changes in weight (more commonly weight gain than loss), dry mouth or throat, dyspepsia, flatulence, gingivitis, nausea, and vomiting can occur. *Haematological*: leucopenia. *Immunological*: fever and flu-like symptoms, infection (especially viral). *Musculoskeletal*: arthralgia, back pain, myalgia, and twitching. *Neurological*: the commonest side effects are ataxia, dizziness, fatigue (dose-related and may settle if doses are reduced), and vertigo. Less commonly, amnesia, convulsions, coordination impairment, dysarthria, headache, insomnia, movement disorders, nystagmus, paraesthesiae, speech disorders. *Ophthalmological*: amblyopia and diplopia. *Psychiatric*: anxiety, confusion, depression, labile affect, hostility. Respiratory: bronchitis, cough, dyspnoea, pharyngitis, and rhinitis.
- *Serious—Dermatological*: angio-oedema and Stevens–Johnson syndrome can occur. *Gastrointestinal*: rarely, hepatitis and pancreatitis have been reported. *Immunological*: rarely patients can develop a hypersensitivity syndrome. *Psychiatric*: suicidal ideation has been reported. *Renal*: acute renal failure is a rarely reported adverse event.

Contraindications

- *Absolute*: hypersensitivity to gabapentin, pregabalin, or any excipient.

1. Gabapentin.

- *Relative*: gabapentin may exacerbate generalized seizures. It should be used with caution in individuals with a history of psychotic illness. Gabapentin is primarily renally excreted, and hence dosing needs to be adjusted, depending on the eGFR: If the eGFR is 50–80 mL/min/1.73 m^2, the dose should be reduced to a maximum of 1.8 g daily; if the eGFR is 30–50 mL/min/1.73 m^2, the dose should be reduced to a maximum of 900 mg daily; if the eGFR is 15–30 mL/min/1.73 m^2, the dose should be reduced to 300 mg on alternate days up to a maximum of 600 mg daily; if the eGFR <15 mL/min/1.73 m^2, the dose should be reduced in proportion to the eGFR. No dose adjustments are required in hepatic impairment.

2. Gabapentin enacarbil.

- *Relative*: no dose adjustment is required in hepatic impairment. Dose adjustment is not necessary for patients with CrCl ≥60 mL/min. For patients with CrCl 30–59 mL/min, the recommended initial dose is 300 mg/day and may be increased to 600 mg/day, as needed. When CrCl is 15–29 mL/min, the recommended dose is 300 mg daily, and 300 mg every other day when CrCl is <15 mL/min.

Use in special populations

- *Elderly*: the elderly are more susceptible to side effects, e.g. falls, tiredness, and weakness. There is also an age-related decline in renal function, and hence lower doses should be used.
- *Pregnancy*: gabapentin and gabapentin enacarbil have not been adequately studied in pregnancy. Animal studies have demonstrated teratogenic effects including delayed ossification, hydroureter, and hydronephrosis, impaired neuronal synapse formation, and skeletal variations; however, studies in humans are still very limited. A few studies have reported potentially increased risk of preterm delivery and low birth weight, but these findings remain to be validated by more robust literature. Use in pregnancy involves weighing up the potential benefits and side effects. The pharmacokinetics of gabapentin do not change during pregnancy.
- *Lactation*: breastfed infants are exposed to gabapentin in maternal milk. An infant can expect to have gabapentin levels of 4–12% that of the mother. There is only limited data on the effects on the infant when nursing mothers take gabapentin, no adverse events have been reported. If used, infants should be monitored for side effects, and an alternative feeding regimen used if these are identified.

Efficacy

- *Epilepsy*: Expert consensus suggests that gabapentin is more effective than placebo as monotherapy in the treatment of focal-onset epilepsy. The SANAD study, a large unblinded trial conducted in the UK, found gabapentin to be significantly less effective than carbamazepine or lamotrigine for focal-onset epilepsy. The efficacy of gabapentin as adjunctive therapy in conjunction with other anti-seizure medications was demonstrated in multicentre placebo-controlled, double-blind, parallel-group clinical trials in adult and paediatric patients (≥ 3 years old) with refractory partial seizures. Increasing efficacy with increasing dose was observed in several of these studies. One study demonstrated that the responder rate (reduction of seizure frequency by more than 50%) was 22% in the gabapentin 900 mg/day group compared to 10.1% in the placebo group ($p = 0.02$).
- *ET*: a double-blind, multiple-dose, placebo-controlled cross-over trial ($n = 25$) of gabapentin found significant improvements in global assessments ($p < 0.05$), observed tremor scores ($p < 0.005$), water pouring scores ($p < 0.05$), and activities of daily living scores ($p < 0.005$). Tremor amplitude scores did not improve in this study. However, amplitudes measured by accelerometry in another RCT ($n = 16$) found gabapentin (1200 mg/day) reduced tremor amplitude at day 15 by 77%.
- *Headache*: a Cochrane review of gabapentin in the prophylaxis of episodic migraine found that, in the pooled analysis, there was no difference between gabapentin and placebo in reducing the frequency of headache at doses ranging from 1200 mg to 2000 mg. There was

no evidence of increasing efficacy with higher doses. When analysed separately, two trials showed a modest benefit of active treatment over placebo. Gabapentin is currently a second-line agent in the UK for migraine prophylaxis. It has also been shown in published case series to be effective in the prophylaxis of SUNCT where it is used as a third-line agent, after lamotrigine and topiramate.

- *Neuropathic pain*: a recent systematic review identified 29 studies involving 3571 participants with various neuropathic pain syndromes treated with gabapentin. Gabapentin showed statistical efficacy (50% pain reduction), compared to placebo, in treating painful diabetic neuropathy (829 participants), with an NNT of 5.8 (95% CI 4.3–9.0), and in treating post-herpetic neuralgia (892 participants), with an NNT of 7.5 (95% CI 5.2–14) for 50% pain reduction. A small study also showed a small benefit from gabapentin treatment in pain relief in patients with fibromyalgia. Two recent systematic reviews have shown that gabapentin is effective at producing good relief from neuropathic pain post-spinal cord injury and in phantom limb pain.
- *RLS*:
  1. Gabapentin: a double-blind, placebo-controlled, cross-over study (*n* = 24) found gabapentin (mean effective dose 1855 mg/day) treatment after 6 weeks reduced the mean RLS rating scale score by 10.5 vs. 2.1 with placebo ($p < 0.001$). Gabapentin also improved sleep quality, reduced periodic leg movements of sleep, and clinical global impression of change.
  2. Gabapentin enacarbil: a 12-week multicentre RCT (*n* = 222) of gabapentin enacarbil found an average difference in International Restless Legs Scale (IRLS) score of −4.0 (95% CI −6.2 to −1.9; $p = 0.0003$). 76% of patients treated were responders, compared to 39% with placebo ($p < 0.0001$). Long-term efficacy and safety were shown in a 52-week extension study (*n* = 573) in patients with moderate-to-severe RLS. Adverse events were reported in 80% of subjects; however, they led to study withdrawal in only 10%. At the end of the study period, subjects had an average difference in IRLS of −15.2, and 85% were Clinical Global Impression–Improvement scale responders.
- *Spasticity*: gabapentin was first trialled as a spasticity therapy in the late 1990s. A handful of small, randomized, placebo-controlled trials and observational studies found it to be effective in treating spasticity secondary to MS or spinal cord injury by various measures (including modest improvements in Ashworth score). In the context of spasticity, there are no systematic reviews, meta-analyses, or comparative studies of efficacy or tolerability available.

Dosing and monitoring

Dosing

Gabapentin

For epilepsy with partial-onset seizures: Start treatment at 300 mg tds, can be titrated up to 600 mg three times daily (for patients 12 years of age and older). Dosages up to 2400 mg/day have been well tolerated.

For post-herpetic neuralgia: Start treatment at 300 mg/day on day 1, 300 mg bd on day 2, and 300 mg tds on day 3. Then gabapentin is increased by 300 mg/day in 2–3 divided doses every 3 days. Dosages up to 3600 mg/day can be tolerated, but doses above 1800 mg/day have not been shown to provide any additional benefit. The maximum time between doses should not exceed 12 h.

For RLS: There is no standardized dosing regimen. Consider starting at 100–300 mg at night and increasing dose by 100–300 mg every 3 days, up to 900 mg TDS.

Gabapentin enacarbil

For post-herpetic neuralgia: Start treatment at 600 mg in the morning for the first 3 days, then increase to 600 mg bd from day 4 onwards. A dose of 1200 mg od offered no additional benefits.

For RLS: 600 mg od at about 5.00 p.m., taken with food. A dose of 1200 mg od offered no additional benefits relative to the 600 mg dose and resulted in increased adverse reactions.

Monitoring

Liver and renal function tests should be performed before starting the medication and yearly thereafter while therapy is continued. Diabetic patients will require close monitoring of blood glucose levels. Weight and BMI will also need to be regularly reviewed.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 2–20 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

- *Gabapentin enacarbil*: in the fed state, it has a bioavailability of 75% (42–65% fasting). It undergoes first-pass hydrolysis, predominantly by enterocytes, to gabapentin. T_{max} of gabapentin is reached in 5–7 h, with steady state reached in 2 days, with daily administration (blood levels of gabapentin enacarbil are very low and thought to be insignificant). The rest of the pharmacokinetic profile is as for gabapentin.
- *Gabapentin*: ~60% of a 300 mg capsule reaches the bloodstream. The bioavailability reduces markedly at higher doses. Food co-ingestion will further reduce the extent of absorption by 25% and delays absorption by 2–3 h. T_{max} occurs at ~2 h; this is faster at larger doses. Steady state is reached in 1–2 days. Less than 3% is protein-bound. The half-life is 5–7 h. Pharmacokinetics are non-linear, due to saturable absorption. Elimination is directly proportional to the eGFR, as there is 100% renal excretion and no hepatic metabolism.

Interactions

See Table 24.25.

Table 24.25 Interactions of gabapentin

Medications which alter gabapentin plasma levels	Medications whose plasma levels are altered by gabapentin
Levels decreased: antacids. Levels increased: cimetidine, naproxen, hydrocodone, and morphine	Levels decreased: pregabalin. Levels increased: felbamate

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Givosiran

Givosiran is a small interfering RNA molecule that degrades aminolevulinate synthase 1 mRNA (an enzyme that is elevated in acute hepatic porphyrias). It was first approved by the FDA and in the EU in 2020. It is delivered by monthly subcutaneous injections . Expert guidance recommends consideration of givosiran in genetically confirmed AHP with frequent, severe attacks (4 or more per year).

Uses

Licensed uses

In the UK/USA

- *Acute hepatic porphyria:* Givosiran is licensed for the treatment of acute hepatic porphyria in individuals aged 12 year and older (UK)/ 18 years and older (USA).

Off-label uses

- There are no off-label uses.

Presentation

- *Trade names*: Givlaari®. Generics are not available.
- *Formulations*: Givosiran is available as a single dose vial, containing 1 mL at a concentration of 189 mg/mL for subcutaneous injection.

Mechanism of action

Givosiran is a double-stranded small interfering RNA (siRNA) that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes, which is elevated in AHP. This reduces the circulating levels of the intermediate products aminolevulinic acid (ALA) and porphobilinogen (PBG), which are neurotoxic.

Toxicity and side effects

- *Common—Dermatological:* Rash, injection site reaction (36% patients). *Gastrointestinal:* Elevated transaminases (3 times upper limit of normal (ULN) 15% onset 3–5 months following initiation), nausea. *Immunological:* Hypersensitivity. *Renal:* Elevated creatinine (reduced GFR) (15%).
- *Serious—Immunological:* Anaphylactic reaction (0.9%).

Contraindications

- *Absolute*: Hypersensitivity to givosiran.
- *Relative*: Givosiran has not been studied in patients with moderate or severe hepatic impairment. No dose reduction is required for renal impairment.

Use in special populations

- *Elderly*: no dose adjustment is required. Use with caution, as the elderly are more prone to side effects and have an age-related impairment in hepatic function.
- *Pregnancy*: No data is available from human studies. In animal studies, administration of givosiran at maternal toxic levels led to increased early absorption post-implantation but did not lead to adverse developmental effects, suggesting there is an indirect risk of increased resorption in animals related to maternal toxicity rather than a direct toxic effect on the fetus. Use of givosiran in pregnancy should only be considered if the potential benefits to the mother outweigh the risks to the fetus.
- *Lactation*: Givosiran is present in mammalian milk, however there is no data in humans. Given the lack of data it may be sensible to temporarily pause breastfeeding during administration of givosiran.

Efficacy

The ENVISION study was a randomized, double-blind, placebo-controlled, multinational study of givosiran in patients with AHP (n = 94). Eligible patients were randomized 1:1 to receive once monthly SC injections of givosiran 2.5 mg/kg or placebo during the 6-month period. Efficacy in the

6-month period was measured by the annualized attack rate (AAR) of composite porphyria attacks and consisted of three components: attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home. AHP patients on givosiran experienced 70% fewer porphyria attacks compared to placebo ($p<0.001$). In addition to its efficacy in reducing attacks and hemin use, givosiran has also been shown to improve quality of life in patients with AHP.

Median reductions from baseline in urinary ALA and PBG of 83.7% and 75.1%, respectively, were observed 14 days after the first dose. Maximal reductions in ALA and PBG levels were achieved around month 3 with median reductions from baseline of 93.8% for ALA and 94.5% for PBG.

Dosing and monitoring

Dosing

Start treatment at 2.5 mg/kg once monthly, administered via subcutaneous injection. Dosing is based on actual body weight. If patients have had clinically relevant transaminase elevations, who have dose interruption and subsequent improvement in transaminase levels, the clinician could consider restarting treatment at 1.25 mg/kg once monthly.

Monitoring

A comprehensive metabolic panel including plasma homocysteine levels (may rise with treatment), urinalysis, urinary protein to creatinine ratio, B_{12}/folate, amylase/lipase should be undertaken before starting givosiran and then every 3 months for the first year. After the first year, repeat the panel at 6 monthly intervals.

Pharmacokinetics and interactions

Pharmacokinetics

Givosiran is rapidly absorbed following subcutaneous injection. Peak plasma concentrations are achieved at 0.5–2 h post-dose. Protein binding is >90%. Givosiran is metabolized by nucleases to several active metabolites. It is rapidly taken up by the liver. The terminal plasma half-life is 5 h. The elimination half-life within the liver is significantly longer (approx. 1 week). There is no accumulation after repeat doses at monthly intervals.

Interactions

See Table 24.26.

Table 24.26 Interactions of givosiran

Medications whose plasma levels are altered by givosiran
Levels increased: drugs which are substrates of CYP1A2 or CYP2D6 isoenzymes e.g. caffeine, clozapine, duloxetine

References

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Glatiramer acetate

This drug, also known as copolymer 1, is a mixture of polypeptides that was first shown to reduce relapse rates in MS in 1995. It remains a first-line treatment option in RRMS. It is an established drug with many years of clinical experience and a good safety profile. Its role has diminished recently with the advent of newer agents, which can be administered orally and are probably more effective at reducing relapses e.g. dimethyl fumarate, but come with the compromise of a worse adverse event profile.

Uses

Licensed uses

In the UK/USA

- *RRMS*: glatiramer acetate is licensed for RRMS. Licensing in the UK requires there to be at least two relapses over the preceding 2 years.
- *Clinically isolated syndrome*: glatiramer acetate is also licensed for patients with a single demyelinating event with an active inflammatory process. In the USA, this requires evidence of MRI features consistent with MS, and, in the UK, this requires that patients be deemed at high risk of developing clinically definite MS.

Off-label uses

- None.

Presentation

- *Trade name*: Brabio®. Copaxone®. Glatopa®. Generics are not available.
- *Formulation*: solution for SC injection in pre-filled syringes: 20 and 40 mg.

Mechanism of action

Glatiramer acetate is a salt mixture of polypeptides consisting of random combinations of four *L*-amino acids. Alanine, glutamate, lysine, and tyrosine are present in specific molar fractions within this mixture. The mechanism of action is complex and not entirely understood but likely involves immune process modulation. The polypeptide mixture is antigenically similar to myelin basic protein and demonstrates strong binding to MHC molecules. It prevents the presentation of myelin antigens to T cells and may also induce and activate glatiramer acetate-specific T helper 2 (Th2) suppressor cells in the periphery that migrate to sites of CNS inflammation, thereby inducing anti-inflammatory cytokine secretion. Glatiramer acetate may also induce T helper 3 (Th3) and T-regulatory cells and downregulate Th1 and Th17 cells. It may also facilitate neuroprotective repair processes including neurotrophic factor secretion, remyelination, and neurogenesis.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension, palpitations, and tachycardia. *Dermatological*: benign skin cancer, ecchymosis, flushing, hyperhidrosis, injection site atrophy and reactions (injection site necrosis in rare cases), pruritus, rash, and urticaria. *Gastrointestinal*: anorexia, constipation, dyspepsia, dysphagia, gastroenteritis, vomiting, and weight gain. *Immunological*: fever, lymphadenopathy, and rigors. *Musculoskeletal*: arthralgia, and back, chest, and neck pain. *Neurological*: dysgeusia, headache, hypertonia, speech disorder, syncope, and tremor. *Ophthalmological*: cataracts and diplopia. *Psychiatric*: anxiety and depression. *Respiratory*: bronchitis, dyspnoea, influenza, otitis media, and rhinitis.
- *Serious—Genitourinary*: urinary retention. *Gastroenterological:* hepatic injury including liver failure and hepatitis with jaundice *Haematological*: leucopenia and thrombocytopenia. *Immunological*: hypersensitivity and an increased risk of infections. *Ophthalmological*: optic atrophy. *Psychiatric*: psychosis.

Contraindications

- *Absolute*: hypersensitivity to glatiramer acetate (or mannitol) and pregnancy.
- *Relative*: the effect of the drug on patients with hepatic and renal impairment has not been studied, and caution with careful monitoring is advised.

Use in special populations

- *Elderly*: glatiramer acetate has not been studied in the elderly.
- *Pregnancy*: Large pregnancy registries have not demonstrated any clear adverse effects on the fetus. Caution is still advised given the lack of long-term data. Glatiramer could be continued if potential benefits outweigh the potential risks of harm.
- *Lactation*: Glatiramer is rapidly broken down in subcutaneous tissue, with minimal active ingredients reaching maternal plasma, urine, or faeces. There have been no studies in breast milk, but it is unlikely that a significant amount will be present, and any residual is likely to be digested by the infant's digestive tract. Most consider glatiramer safe to use by nursing mothers.

Efficacy

Results from multiple placebo-controlled trials and a systematic review of 6 RCTs support the efficacy of glatiramer acetate, which decreases frequency of relapses and burden and activity of disease on MRI. Glatiramer acetate was shown to reduce the ARR by ~30% in pivotal and subsequent trials. Another study found that time to development of a second exacerbation was substantially extended in patients receiving glatiramer acetate compared to placebo. In addition, patients receiving treatment had fewer new T2 lesions and lower baseline-adjusted T2-lesion volume at the last observation. The total cumulative number of T1 Gd-enhancing lesions and the total number of confirmed relapses were also shown to be lower in other studies on glatiramer acetate, further validating its efficacy. In an extension study, the beneficial effects of glatiramer acetate continued for 15 years of treatment. Overall efficacy is considered broadly equivalent to IFN-β-1a and IFN-β-1b (BEYOND trial).

Dosing and monitoring

Dosing

Glatiramer acetate is administered as a subcutaneous injection, either 20 mg od or 40 mg 3 times weekly (at least 48 h apart).

Monitoring

No specific monitoring is required. Patients should be informed that anxiety, chest pain, dsypnoea, flushing, palpitations, tachycardia, throat constriction, and urticaria may occur within seconds to minutes of initial injections and are typically short-lived without any complications. No data exist to support the need for a washout period before switching to an alternative immunomodulatory agent. It is generally stopped for 4–6 weeks prior to the initiation of natalizumab, but no washout period is needed when switching to IFN-β or fingolimod.

Pharmacokinetics and interactions

Pharmacokinetics

There is limited information on the absorption, distribution, or excretion of this drug, because there are no accurate *in vivo* assays for measuring glatiramer acetate or its breakdown products. *In vitro* studies suggest that metabolism occurs at the site of injection, with the active substance readily absorbed and a significant portion of the dose rapidly degraded to smaller fragments in subcutaneous tissue.

Interactions

None; however, monitor concurrent use of phenytoin and carbamazepine carefully given the potential for glatiramer acetate to impact the distribution of protein-bound substances.

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Glyceryl trinitrate

GTN is an organic nitrate. It was first synthesized in 1846. It is widely used as a buccal spray in the management of angina pectoris and has been marketed in the UK since the 1930s. It is used off licence as an infusion for the management of severe hypertension in acute stroke. Trials are ongoing as to whether its use in this setting has a beneficial effect on functional outcomes.

Uses

Licensed uses

In the UK/USA
GTN has no licensed neurological uses.

Off-label uses

GTN infusion can be used in acute stroke if there is evidence of malignant hypertension or to lower the BP to <185/110mmHg in patients with ischaemic stroke who are potential candidates for alteplase. The effectiveness of a GTN patch to lower the BP in lesser degrees of hypertension is currently under assessment in clinical trials.

Presentation

- *Trade names*: Nitrocine® and Nitronal®. Generics are available.
- *Formulations*: GTN is available in both oral and parenteral forms; in the context of acute ischaemic stroke, only an IV infusion is routinely used. This is available at concentrations of 1 mg/mL and 5 mg/mL, in 5 mL and 10 mL vials for further dilution.

Mechanism of action

GTN is an organic nitrate that releases NO following enzymatic denitration. NO has several important functions, including relaxation of vascular smooth muscle cells via the activation of soluble guanylate cyclase and the formation of cyclic guanosine monophosphate (GMP). NO also inhibits platelet aggregation and leucocyte–endothelial interactions. At high doses, nitrates produce arterial vasodilation, reducing systemic vascular resistances, and hence rapid BP reduction.

Toxicity and side effects

- *Common—cardiovascular*: palpitations, paradoxical bradycardia, postural hypotension, syncope, and tachycardia. *Dermatological*: diaphoresis, flushing, and rash. *Gastrointestinal*: abdominal pain, heartburn, nausea, and vomiting. *Haematological*: anaemia, thrombocytopenia. *Immunological*: allergic reaction. *Neurological*: dizziness, headache, and muscle twitching.
- *Serious—cardiovascular*: crescendo angina, severe hypotension, and cardiovascular collapse. *Immunological*: anaphylaxis. *Haematological*: methemoglobinemia.

Contraindications

- *Absolute*: hypersensitivity to nitrates, hypotensive conditions (systolic BP <100) and hypovolemia, hypertrophic cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis, toxic pulmonary oedema, raised ICP (not due to malignant hypertension), marked anaemia,
- *Relative*: use with caution in severe renal impairment and/or severe hepatic impairment, hypothermia, and hypothyroidism.

Use in special populations

- *Elderly*: no additional dose adjustments are required. The rate of infusion needs to be titrated to individual response.
- *Pregnancy*: the safety of nitrates in pregnancy has not been established. They should only be given if benefits outweigh risks.
- *Lactation*: the safety of nitrates in nursing mothers has not been established. They should only be given if the benefits outweigh the risks.

Efficacy

A Cochrane review has analysed evidence from 12 small trials, which set out to investigate whether BP modification improved outcomes in either acute ischaemic or haemorrhagic stroke. There was insufficient evidence to demonstrate any difference in functional neurological outcomes. Several larger studies are currently ongoing and will hopefully provide results to guide management in this currently controversial area. In addition, the Rapid Intervention with Glyceryl Trinitrate in Hypertensive stroke trial assessed the safety and efficacy of transdermal GTN in the management of acute stroke. A GTN patch or placebo was administered by paramedics to individuals with acute stroke (<4 h since symptom onset). Functional outcomes were not improved by this intervention.

Dosing and monitoring

Dosing

There are no specific dosing instructions provided by manufacturers for this indication. Start treatment at 10–25 micrograms/min, depending on local hospital protocols; this can be increased in increments of 5–10 micrograms, until a desired BP is reached or GTN is no longer tolerated (usually due to headache). The maximum rate is 400 micrograms/min.

Monitoring

Regular monitoring of BP and heart rate is required.

Pharmacokinetics and interactions

Pharmacokinetics

GTN is metabolized hepatically by a reductase to dinitrate and mononitrate. It then undergoes glucuronidation. Spontaneous hydrolysis in the plasma also occurs. The half-life is usually 1–3 min. The metabolites are predominantly eliminated by the renal tract.

Interactions

See Table 24.27.

Table 24.27 Drug interactions of GTN

Pharmacodynamic interactions
With other antihypertensives, e.g. ACE inhibitors: enhanced hypotensive effect
With heparin: reduced anticoagulant effect of heparin.
With corticosteroids and NSAIDs: antagonism of hypotensive effect

References

Bath PM, Scutt P, Anderson CS, *et al.* Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomized, sham-controlled, blinded, phase 3 trial. *Lancet* 2019;393(10175):1009–20.

Geeganage C, Bathj PM. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev* 2008;4:CD000039.

Gray LJ, Sprigg N, Rashid PA, *et al*. Effect of nitric oxide donors on blood pressure and pulse pressure in acute and subacute stroke. *J Stroke Cerebrovasc Dis* 2006;15(6):245–9.

Kobayashi A, Czkonkowska A, Grabska K, *et al*. Efficacy of Nitric Oxide in Stroke—a randomized trial. Characteristics of patients recruited in Poland. *Neurol Neurochir Pol* 2008;42(2):99–104.

Rashid P, Weaver C, Leonardi Bee J, *et al*. The effects of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure, cerebral and cardiac hemodynamics, and plasma nitric oxide levels in acute stroke. *J Stroke Cerebrovasc Dis* 2003;12(3):143–51.

Haem-like therapies

Hemin therapies, most commonly in the form of lyophilized hematin (Panhematin®) and heme arginate (Normosang®), are used in the management of acute attacks of hepatic porphyrias. Heme arginate was first marketed in the UK in 1999. These agents are more effective than carbohydrate loading and should be started as soon as possible in the management of an acute attack.

Uses

Licensed uses

In the UK

- *Inborn errors of metabolism*: heme arginate (Normosang®) is licensed for the treatment of acute porphyrias (acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria) in individuals of all ages.

In the USA

- *Inborn errors of metabolism*: lyophilized hematin (Panhematin®) is licensed for the treatment of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women in individuals aged 16 years and older.

Off-label uses

- Prophylactic treatment in the management of acute porphyrias. Panhematin® is also used off licence in the management of other acute porphyrias.

Presentation

- *Trade names*: Normosang® and Panhematin®. Generics are not available.
- *Formulations*: Normosang® is available as a concentrate for IV infusion, in 10 mL ampoules (25 mg/mL). Panhematin® is available as a powder for IV infusion after reconstitution in vials containing 350 mg of hemin.

Mechanism of action

In the acute porphyrias, there is reduced activity or deficiency of one of a number of enzymes involved in haem synthesis, resulting in a deficiency in haem and a build-up of toxic precursors. IV haem-like compounds hematin and heme arginate are believed to act by replenishing the depleted haem pool and thereby initiating negative feedback processes, which suppress hepatic aminolevulinate synthase activity, an enzyme important in the generation of porphyrins and other toxic haem precursors.

Toxicity and side effects

- *Common—Immunological:* fever, *Neurological*: headache.
- *Serious—Dermatological*: rarely anaphylaxis and hypersensitivity reactions. *Haematological*: thrombophlebitis and venous thrombosis are common and are probably the result of degradation products which form rapidly *in vitro* when lyophilized hemin is reconstituted with sterile water.

Contraindications

- *Absolute*: hypersensitivity to the drug to be used.
- *Relative*: avoid concurrent anticoagulant therapy. Studies have not been performed in patients with hepatic or renal impairment; hence these drugs should only be used with caution in these patient groups.

Use in special populations

- *Elderly*: there are no data on the safety and efficacy of heme arginate in patients above 65 years of age; use with caution.
- *Pregnancy*: limited data is available, and the manufacturer advises to avoid. However, experience indicates that heme arginate can be administered safely during pregnancy. Use if the benefits outweigh the risks of no treatment.
- *Lactation*: no information is available as to whether haem-like drugs are excreted in breast milk; the manufacturer advises to avoid use in nursing mothers.

Efficacy

There are many uncontrolled clinical studies suggesting a favourable clinical response to hemin treatment in the management of acute porphyrias; however, only a few placebo-controlled trials have been conducted. A double-blind, placebo-controlled trial of hemin therapy in 12 patients with acute porphyria showed striking decreases in urinary porphobilinogen excretion and trends in clinical benefit (less pain, decreased need for pain medication, and shortened hospital stays) in patients treated with hemin.

A larger, but uncontrolled, study of 22 patients with acute attacks of porphyria who received heme arginate treatment within 24 h of admission showed that all patients responded to treatment, as demonstrated biochemically by a decrease in mean urinary excretion of porphobilinogen and ALA levels and clinically by the fact that hospitalization was <7 days in 90% of cases. A growing body of evidence has led to the current consensus that early initiation of IV hemin treatment in acute attacks of porphyria is associated with improved outcomes.

Dosing and monitoring

Dosing

Start treatment as soon as acute porphyria is recognized.

- Normosang®: administer 3 mg/kg (maximum 250 mg daily) in 100 mL of 0.9% saline over 30 min IV od for 4 days. Clinical improvement is often rapid and usually evident within 1–2 days. The vein should be flushed with 100 mL of 0.9% of NaCl after infusion.
- Panhematin®: administer 1–4 mg/kg/day of hematin—select the dose, depending on the severity of the attack; in very severe cases, a further dose can be given after 12 h (maximum 6 mg/kg/day). The powder is reconstituted with 43 mL of sterile water; hence 1 mg of hematin is equivalent to 0.14 mL of reconstituted Panhematin®. The dose should be administered over 10–15 min by IV infusion, and given for 3–14 days, depending on clinical response. The vein should be flushed with 100 mL of 0.9% of NaCl after infusion.

Monitoring

During treatment with haem-like therapies, patients should be monitored closely for complications of acute porphyria, hypersensitivity reactions, and thrombophlebitis. Serial urinary levels of ALA, porphobilinogen, and coproporphyrin may also aid recognition of biochemical response to treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Normosang®: Limited data are available from pharmacokinetic studies; in healthy individuals and patients with porphyria, the elimination half-life of heme arginate ranges from 9 h to 12.5 h. After repeated infusions, the elimination half-life increases (18 h after four infusions). The pharmacokinetics of Panhematin® have not been defined.

Interactions

See Table 24.28.

Table 24.28 Interactions of haem-like therapies

Medications whose plasma levels are altered by Normosang®
Levels decreased: barbiturates, corticosteroids, and the oral contraceptive pill

No interactions have been reported with Panhematin®.

References

Herrick AL, McColl KE, Moore MR, *et al*. Controlled trial of haem arginate in acute hepatic porphyria. *Lancet* 1989;1(8650):1295–7.

Marsden JT, Rees DC. A retrospective analysis of the outcome of pregnancy in patients with acute porphyria. *J Inherit Metab Dis* 2010;33(5):591–6.

Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153(17):2004–8.

Idarucizumab

Idarucizumab is a monoclonal antibody, designed as a specific reversal agent for dabigatran. It can be used when rapid reversal of dabigatran is required e.g. in the case of life-threatening bleeding. Its clinical effect lasts for up to 24 h, after which dabigatran can be restarted as required. It was first approved for use by the FDA in 2015, and was first licensed for use in the UK in 2016.

Uses

Licensed uses

In the UK/USA

- Idarucizumab is licensed for urgent reversal for surgery or procedures, or treatment of life-threatening or uncontrolled bleeding in patients treated with dabigatran (Pradaxa®) in individuals aged 18 years and older.

Off-label uses

- None

Presentation

- *Trade names*: Praxbind ®. Generics are not available.
- *Formulations*: Idarucizumab is available as a single use vial containing 2.5 mg of idarucizumab in 50 mL.

Mechanism of action

Idarucizumab is a specific reversal agent for dabigatran (reversible thrombin inhibitor). It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its acylglucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, thereby neutralizing their anticoagulant effect.

Toxicity and side effects

- *Common—Gastrointestinal:* constipation. *Immunological:* pyrexia. *Metabolic:* hypokalaemia. *Neurological:* delirium and headache.
- *Serious—Cardiovascular:* Thromboembolic events.

Contraindications

- *Absolute:* None.
- *Relative*: No dose adjustments are required in hepatic or renal impairment.

Use in special populations

- *Elderly*: no differences were noted between younger and older patients in clinical trials. No dose adjustment is required.
- *Pregnancy*: No data are available from animal or human studies. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: No data are available from animal or human studies. It is not known whether idarucizumab is present in milk. Consider temporarily using an alternative method of feeding if nursing mothers use idarucizumab.

Efficacy

Approval was granted based on healthy volunteer data from three randomized, placebo-controlled trials with a total of 283 subjects. Real world data was utilized from the RE-VERSE AD trial, which was a prospective multicentre, open-label study of idarucizumab (n = 503). The primary endpoint was the maximum percentage reversal of the pharmacodynamic anticoagulant effect of dabigatran within 4 h after the administration of idarucizumab, based on determination of diluted thrombin time (dTT) or ECT. This study demonstrated that the median percentage reversal of dabigatran was 100% based on either the diluted thrombin time or the ECT. In this study, the median time to cessation of bleeding was 2.5 h for patients with uncontrolled bleeding.

Dosing and monitoring

Dosing

Administer 5 g as a bolus injection.

If reappearance of clinically relevant bleeding together with elevated coagulation parameters is observed after administration of 5 g idarucizumab, an additional 5 g dose of idarucizumab may be considered. The safety and effectiveness of repeat treatment with idarucizumab has not been established.

Monitoring

Routine monitoring is not required.

Pharmacokinetics and interactions

Pharmacokinetics

In healthy subjects aged 45 to 64 years, the plasma concentrations of unbound dabigatran were reduced to below the lower limit of quantification immediately after the administration of 5 g idarucizumab. Subjects' dTT, ECT, aPTT, thrombin time (TT), and activated clotting time (ACT) parameters returned to baseline levels. Reduction of dabigatran plasma concentration was observed over the entire observation period of at least 24 h. No changes in the pharmacokinetics or pharmacodynamics of dabigatran were noted upon re-initiation 24 h after the administration of idarucizumab. Monoclonal antibodies are metabolized into smaller peptides or amino acids independent of the hepatic CYP450 system. The terminal half-life of idarucizumab is 10.3 h.

Interactions

There are no clinically significant interactions.

References

Stone L, Merriman E, Hanna M, *et al*. Retrospective analysis of the effectiveness of a reduced dose of Idarucizumab in dabigatran reversal. *Thromb Haemost* 2022;122(7):1096–103.

Pollack C, Reilly P, Van Ryn J, *et al*. Idarucizumab for dabigatran reversal—full cohort analysis. *NEJM* 2017;377(5):431–41.

Pollack C, Reilly P, Eikelboom J, *et al*. Idarucizumab for dabigatran reversal. *NEJM* 2015;373(6):511–20.

Intravenous immunoglobulin

IVIg is the pooled, highly purified IgG antibody from the serum of over a thousand human donors. It was first used in the 1950s to treat immunodeficiency syndromes. It is currently widely used to treat a variety of autoimmune conditions.

Uses

IVIg is used as an acute, first-line treatment in a wide range of autoimmune conditions, and as maintenance therapy in chronic disease poorly responsive to alternative therapies. Licensing laws vary between countries and formulations. A summary (non-exhaustive) of its uses are given below:

- Autoimmune limbic encephalitis.
- CANOMAD (first-line, acute).
- CIDP (first-line, acute, or chronic).
- Guillain–Barré syndrome (first-line, acute).
- LEMS (refractory cases).
- MMN with conduction block (first line).
- MG (acute or chronic).
- Neurolupus.
- NMO (second line).
- PM (refractory cases).
- DM (refractory cases).
- Sjögren's syndrome.
- Stiff person syndrome (refractory cases).
- TM (refractory cases).

In the UK, these indications are prioritized by a colour-coding scheme (red, blue, or grey in descending order), based on availability of alternative treatments and the strength of clinical evidence.

Presentation

- *Trade name*: Aragam®, Bivigam®, Flebogamma®, Gammagard S/D®, Gammaked®, Gammaplex®, Gamunex®, Intratect®, Kiovig®, Octagam®, Privigen®, and Vigam®. Generics are not available.
- *Formulation*: IVIg is available as an infusion of 5% protein (Aragam®, Flebogamma®, Gammagard S/D®, Gammaplex®, Intratect® Octagam®, and Vigam®), or 10% protein (Bivigam®, Gamunex®, Kiovig®, and Privigen®). 5% protein infusion: 0.5 g, 1 g, 2 g, 2.5 g, 5 g, 10 g, and 20 g. 10% protein infusion: 1 g, 5 g, 10 g, 20 g, and 30 g.

Mechanism of action

The mechanism of action of IVIg remains unclear after many decades of use and experience from both animal and human studies. Its action is paradoxical in that many of the diseases treated with IVIg themselves owe their pathology to the IgG molecule. Several mechanisms have been proposed: $F(ab')_2$-dependent effects (involving the fragment antigen-binding region of the molecule) include the blockade of cell–cell interactions, as IVIg binds cellular surface receptors; neutralization of cytokines and autoantibodies; antibody-dependent cytotoxicity which kills target cells; and scavenging of anaphylatoxins C3a and C5a. Fc-dependent mechanisms (involving the fragment crystallizable region of the IgG molecule) include expansion of regulatory T-cell populations, modulation of dendritic cells, and the blockade of immune complex binding, thereby blocking activating receptors on target cells.

Toxicity and side effects

- *Common—cardiovascular*: hypertension and palpitations. *Dermatological*: injection site reaction, rash. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, and vomiting. *Immunological*: fever, flushing, malaise, rigors. More likely to be severe in patients with pre-existing, chronic, or inadequately treated infections. *Musculoskeletal*: arthralgia and myalgia. *Neurological*: headache. *Renal*: hyponatraemia.
- *Serious—cardiovascular*: hypertension, hypotension, MI. *Dermatological*: erythema multiforme. *Genitourinary*: acute kidney injury. *Haematological*: haemolytic anaemia. *Immunological*: anaphylaxis and hypersensitivity (especially in IgA-deficient patients). *Infectious*: there is a theoretical risk of seroconversion for blood-borne viruses, i.e. hepatitis and HIV. *Neurological*: aseptic meningitis syndrome and stroke. *Respiratory*: VTE.

Contraindications

- *Absolute*: fructose intolerance, hypersensitivity, prolinemia, and IgA deficiency.
- *Relative*: the risk of acute kidney injury is increased with preparations with added sucrose, underlying renal disease, diabetes mellitus, advanced age, volume depletion, sepsis, paraproteinaemia, and co-prescription of nephrotoxic drugs. Caution is advised in patients with pre-existing renal impairment. No dose adjustment is required in hepatic impairment.

Use in special populations

- *Elderly*: a lower concentration and/or slower rate of IVIg infusion should be used in elderly patients, due to the increased risk of renal impairment.
- *Pregnancy*: IVIg crosses the placenta. Experience suggests that there are no harmful effects on the course of pregnancy or the fetus, but caution is advised.
- *Lactation*: IVIg is excreted into breast milk. Small case series have not demonstrated any serious adverse effects in infants of breastfeeding mothers treated with IVIg. Caution during breastfeeding is recommended.

Efficacy

IVIg is used to treat a large number of autoimmune disorders. For a discussion with regard to the evidence base for use in these indications, please see the individual conditions.

Dosing and monitoring

Dosing

Regimens vary according to indications and preparations, but typically IVIg is prescribed at 0.4 g/kg/day over 5 days (i.e. 2 g/kg in total). An initial rate of infusion of 0.01–0.02 mL/kg/min is typical for 5% IVIg for the first 30 min. This can be increased gradually, as tolerated, to a maximum of 0.1 mL/kg/min. This is based on dosing regimens used in initial experience of the drug, but optimum dosing regimens and durations of therapy are yet to be established. Paracetamol, antihistamines, and glucocorticoids are often administered as pre-medications for their antipyretic and anti-inflammatory properties for IVIg-naïve patients or on changing brands. Good hydration should be ensured prior to commencing IVIg infusion to avoid thrombotic and nephrotoxic complications of therapy.

Monitoring

Serum IgA levels and renal function should be checked prior to treatment initiation. Blood-borne viral serology may be taken prior to the first treatment, as IVIg is a blood product and there is a rare potential risk of viral seroconversion following infusion. Patients should be monitored closely during the first dose for infusion reactions. These are more likely during the first dose, with high infusion rates and with long delays since the last dose. If side effects occur, the infusion should be stopped, and the patient appropriately treated. Depending on the nature of the side effect, the infusion can be recommended at a lower rate and increased as tolerated. Renal function and FBC should be monitored following a course of treatment.

Pharmacokinetics and interactions

Pharmacokinetics

The immunoglobulin is distributed rapidly within the plasma and extracellular fluid, reaching a steady state at 3–5 days. Immunoglobulins and their complexes are mostly broken down by the reticuloendothelial system. The half-life varies between patients and preparations. The mean half-life is 21.7 days, following the first dose of a commonly used preparation.

Interactions

IVIg may impair the immune response to live virus vaccines. These should only be given 3 weeks before, or 3 months after, IVIg. There are no other specific interactions.

References

Elovaara I, Apostolski S, van Doorn P, *et al*. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. *Eur J Neurol* 2008;15(9):893–908.

Patwa HS, Chaudhry V, Katzberg H, *et al*. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2012;78(13):1009–15.

Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol* 2013;13(3):176–89.

Istradefylline

Istradefylline received FDA approval to treat motor fluctuations in PD in 2019. Unlike COMTi and MAOi, which are the other main drug classes used for this indication, it has a unique mechanism of action mediated through inhibition of adenosine A2A receptors. It is effective at reducing 'OFF' periods and is typically well tolerated.

Uses

Licensed uses

In the USA (istradefylline is not approved for use in the UK)

- *PD*: istradefylline is licensed for the treatment of 'OFF' episodes in patients with PD, as an adjunct to levodopa therapy, in individuals aged 18 years and older.

Off-label uses

- None.

Presentation

- *Trade names*: Nourianz®. Generics are not available.
- *Formulations*: istradefylline is available as 20 and 40 mg tablets.

Mechanism of action

The exact mechanism of action in the treatment of PD is unknown. Istradefylline is a selective adenosine A2A receptor antagonist. A2A receptors have a relatively restricted presentation in the striatum, specifically on GABAergic projection neurons. Reduced GABA may suppress the indirect pathway resulting in a pro-kinetic effect and improved parkinsonian symptoms.

Toxicity and side effects

- *Common—Dermatological*: rash. *Gastrointestinal*: constipation, diarrhoea, and nausea. *Neurological*: dizziness, dyskinesia, and insomnia. *Psychiatric*: hallucinations and impulse control disorders. *Respiratory:* Upper respiratory tract inflammation.
- *Serious*—None.

Contraindications

- *Absolute*: known hypersensitivity to istradefylline or its excipients. Severe hepatic impairment.
- *Relative*: Psychotic behaviour, abnormal thinking and behaviour was seen in 2% of patients taking 40 mg of istradefylline vs. 1% of patients on placebo, i.e. only a low possible risk. Use a reduced dose (20 mg) in individuals with moderate hepatic impairment. No dose adjustment is required in renal impairment.

Use in special populations

- *Elderly*: no dose adjustment is required in the elderly population.
- *Pregnancy*: There are no human data on the use of istradefylline in pregnancy. Teratogenicity was noted in animal studies at clinically relevant doses; hence, use in pregnancy is contraindicated.
- *Lactation*: There are no human data on the presence of istradefylline in human breastmilk. Istradefylline was present in the milk of lactating rats at concentrations up to 10 times higher than that seen in plasma; hence, it is likely that it will also be present in breastmilk. Use only if the potential benefits outweigh the risks of treatment.

Efficacy

A pooled analysis of 2,719 patients from eight separate studies was published in 2021. OFF time at week 12 reduced by 0.38 h with 20 mg, and 0.45 h with 40 mg of istradefylline, compared to the change seen with placebo ($p < 0.0001$).

Dosing and monitoring

Dosing

Start treatment at 20 mg once daily and increase to 40 mg once daily based on clinical response and tolerability.

Monitoring

None required

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is not known. T_{max} is ~4 h. T_{max} is 1 h less and C_{max} 1.64 times higher when taken with a high-fat meal. 98% is protein-bound. Istradefylline is predominantly metabolized by hepatic CYP1A1 and CYP3A4 enzymes. Metabolites are effectively inactive. 48% of the drug is eliminated in the faeces and 39% in the urine. The terminal half-life is 83 h.

Interactions

See Table 24.29.

Table 24.29 Interactions of istradefylline

Medications which alter istradefylline plasma levels	Medications whose plasma levels are altered by istradefylline	Pharmacodynamic interactions
Levels increased: CYP3A4 inhibitorse.g.itraconazole, clarithromycin. Levels decreased: CYP3A4 inducerse.g.carbamazepine, phenytoin. Tobacco.	Levels increased: Atorvastatin and digoxin.	With other dopaminergic medications: Dyskinesia and other dopaminergic side effects.

References

Hauser R, Hattori N, Fernandez H, *et al.* Efficacy of istradefylline, an Adenosine A2A receptor antagonist, as adjunctive therapy in Parkinson's disease: a pooled analysis of 8 Phase 2b/3 trials.

Labetalol

Labetalol is an antagonist of both β-adrenergic and α1-adrenergic receptors. It is used in the treatment of hypertension associated with a variety of conditions and was first marketed in the UK during the 1980s.

Uses

Licensed uses

In the UK/USA
There are no licensed neurological uses.

Off-label uses

Labetalol infusion can be used in acute stroke if there is evidence of malignant hypertension or to lower the BP to <185/110mmHg in patients with ischaemic stroke who are potential candidates for alteplase.

Presentation

- *Trade name*: Trandate®. Generics are available.
- *Formulations*: labetalol is available in both PO and parenteral forms. In the context of acute ischaemic stroke, only the IV route is routinely used. This is available as a solution at a concentration of 5 mg/mL in 4 mL, 20 mL, and 40 mL vials.

Mechanism of action

Labetalol acts by blocking α- and β-adrenergic receptors, resulting in decreased peripheral vascular resistance, while preventing the reflex tachycardia, thereby maintaining a low BP.

Toxicity and side effects

- *Common—Cardiovascular*: bradycardia, postural hypotension, and syncope (avoid the upright position during, and for 3 h after, IV administration). *Dermatological*: flushing and rash. *Gastrointestinal*: epigastric pain. *Immunological*: allergic reaction. *Neurological*: dizziness and headache.
- *Serious—Gastrointestinal*: hepatocellular damage.

Contraindications

- *Absolute*: hypersensitivity to labetalol, uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease. Avoid in those with hepatic impairment, as severe hepatocellular injury has been reported.
- *Relative*: untreated phaeochromocytoma, first-degree AV block, asthma, or other obstructive airway disease. No dose adjustments are routinely recommended in hepatic or renal impairment. However, labetalol should be used with caution with hepatic impairment, as hepatocellular injury can occur, and labetalol is predominantly eliminated in the urine; hence dose adjustment may be required in renal impairment.

Use in special populations

- *Elderly*: the elderly are more prone to pre-existing cardiovascular disease and are more at risk of postural hypotension and falls. Labetalol should be used with caution in this group.
- *Pregnancy*: no teratogenic effects have been identified in animal studies; however, labetalol crosses the placental barrier and will increase the risk of fetal bradycardia, distress, respiratory depression, hypoglycaemia, and both cardiac and respiratory complications when used late in labour for the neonate post-natally. Current studies have not found an increased risk for fetal growth restriction or preterm delivery with concurrent gestational labetalol exposure. There is not enough data on miscarriage, stillbirth, or neurodevelopmental outcomes at this time. It should only be given if the benefits outweigh the risks.
- *Lactation*: No special precautions are required. Only low levels of labetalol have been found to cross the breast milk barrier and are not expected to cause adverse effects in infants.

Efficacy

The CHHIPS trial was a double-blind RCT of 179 patients that looked at the acute treatment with labetalol or lisinopril for those with systolic BP >160 mmHg in the context of acute ischaemic and haemorrhagic stroke. Within 36 h of symptom onset, patients were either assigned to oral labetalol, lisinopril, or placebo, or to IV labetalol, sublingual lisinopril, or placebo if suffering from dysphagia. The primary outcome assessed was mortality or dependency at 14 days post-symptom onset; this occurred in 61% of patients who were actively managed, and 59% of patients treated with placebo (RR 1.03, 95% CI 0.80–1.33; $p = 0.82$). No acute neurological deterioration was noted in the actively treated group, despite the significantly higher reduction in systolic BP. Importantly, at 3 months post-stroke, the rates of mortality were halved in those who were actively treated (HR 0.40, 95% CI 0.2–1.0; $p = 0.05$). Early lowering of the BP with lisinopril and labetalol after acute stroke seems to be a promising approach to reduce mortality and potential disability.

Dosing and monitoring

Dosing

There are no specific dosing instructions provided by manufacturers for this indication. Treatment can be in the form of repeated IV boluses or IV infusion. IV bolus: give 10–20 mg over 10 min (consider higher doses if systolic BP >230 mmHg or diastolic BP >120 mmHg); this can be repeated or doubled every 10 min up to a maximum dose of 150–200 mg. An IV infusion can be used initially or after repeat boluses. Start the infusion at a rate of 2 mg/min, and titrate up to 8 mg/min, as required.

Monitoring

Patients should have an ECG performed at baseline to look for any form of heart block. They should then be attached to a cardiac monitor to allow frequent monitoring of BP and heart rate.

Pharmacokinetics and interactions

Pharmacokinetics

Labetalol binds to plasma proteins (50%) and is extensively metabolized in the liver to produce inactive glucuronide metabolites, excreted in the urine (50%) and bile. The plasma half-life is ~4 h.

Interactions

See Table 24.30.

Table 24.30 Interactions of labetalol

Medications which alter labetalol plasma levels	Medications whose plasma levels are altered by labetalol	Pharmacodynamic interactions
Levels increased: cimetidine	Levels increased: imipramine	With other hypotensive agents, e.g. ACE inhibitors: enhanced hypotensive effect With antiarrhythmics/ calcium channel blockers: increased myocardial depression/ risk of bradycardia/ AV block With hypoglycaemic agents: beta-blockers may enhance hypoglycaemic effects of insulin With clonidine: risk of withdrawal hypertension With crizotinib, fingolimod, and mefloquine: increased risk of bradycardia With ergotamine and methysergide: increased risk of peripheral vasoconstriction With heparin: reduced anticoagulant effect. With corticosteroids and NSAIDs: reduced hypotensive effect

References

Potter JF, Robinson TG, Ford GA, *et al*. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* 2009;8(1):48–56.

Lacosamide

Lacosamide was first marketed in the UK as an ASM in 2008. Its main advantage is its paucity of pharmacokinetic interactions, and its main disadvantage is a high incidence of gastrointestinal side effects.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: lacosamide is licensed for treatment as a monotherapy or adjunctive therapy of focal-onset seizures in individuals aged 4 years and older in the UK, and aged 1 month of age and older in the USA. In the UK and the US, it is also licensed for treatment as an adjunct of primary generalized tonic–clonic seizures in adults, adolescents, and children 4 years or older with idiopathic generalized epilepsy.

Off-label uses

- Status epilepticus.

Presentation

- *Trade names*: Vimpat®. Generics are not available.
- *Formulations*: lacosamide is available as a film-coated tablet, a solution for IV infusion, and a syrup. Film-coated tablet: 50 mg, 100 mg, 150 mg, and 200 mg. Solution for infusion: 10 mg/mL in 20 mL vials. Syrup: 10 mg/mL.

Mechanism of action

The precise mechanism of action of lacosamide is poorly understood. *In vitro* studies have shown that the compound selectively enhances slow inactivation of voltage-gated sodium channels, thereby stabilizing neuronal membranes and inhibiting neuronal depolarization.

Toxicity and side effects

- *Common—Dermatological*: pruritus and rash can occur. *Gastrointestinal*: constipation, flatulence, nausea, and vomiting. *Neurological*: dizziness and headache are very common. Fatigue, impaired concentration and memory, insomnia, tremor, and nystagmus are common. *Ophthalmological*: blurred and double vision. *Psychiatric*: confusion and depression.
- *Serious—Cardiovascular*: prolongation of the PR interval, which can lead to arrhythmia, bradycardia, and heart block. *Dermatological*: rarely angio-oedema. *Immunological*: rarely a multiorgan hypersensitivity reaction can occur. *Psychiatric*: psychosis and suicidal ideation have been reported.

Contraindications

- *Absolute*: hypersensitivity to lacosamide or its excipients, and second-/third-degree heart block.
- *Relative*—severe cardiac disease, conduction abnormalities, elderly, and co-administration with drugs that can prolong the PR interval.

It is recommended to use lacosamide with caution in severe hepatic impairment, although there is a lack of clinical data in this population. Dosages of patients with mild to moderate hepatic impairment should be reduced by 25%, with a maximum dose of 300 mg/day. A maximum of 250 mg/day is recommended in late-stage renal failure with an eGFR <30 mL/min/1.73 m².

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and benefit from lower dosing regimens.
- *Pregnancy*: lacosamide has not been adequately studied in pregnancy. Animal studies have demonstrated teratogenic effects; however, there are no studies in humans. Use in pregnancy involves weighing up the potential benefits and side effects. It is unknown if the pharmacokinetics of lacosamide change during pregnancy.
- *Lactation*: A maternal dosage of 200 mg will produce low levels of lacosamide in breast milk. Maternal dosage up to 400 mg has not been shown to adversely affect development in infants who were breastfed for 7 to 9 months.

Efficacy

The efficacy of lacosamide has mainly been explored in the context of refractory epilepsy. A recent multicentre, double-blind, placebo-controlled trial of patients with focal-onset epilepsy already on two or more ASMs showed that the median percentage reduction in seizure frequency was 35% and 36%, respectively, for 200 mg/day and 400 mg/day dosing protocols, compared to 20% for placebo. No added benefit has been subsequently shown at higher doses.

Dosing and monitoring

Dosing

For the treatment of epilepsy, start treatment at 50 mg bd. This can be increased by 50 mg bd in 1–2 weekly intervals to a recommended maximum dosage of 200 mg bd. Enteral and IV formulations are bioequivalent.

Monitoring

Liver and renal function testing should be performed prior to commencing therapy and then yearly while treatment is ongoing. A baseline ECG is recommended, particularly in the elderly, to rule out heart block.

Therapeutic drug monitoring

Optimum seizure control when used in monotherapy occurs at plasma concentrations of 10–20 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 100%. This is unaffected by food co-ingestion. T_{max} is at 1–2 h post-dose. Steady-state plasma levels are reached at 2–3 days. The pharmacokinetics are linear, and <15% of the compound is protein-bound. The elimination half-life is 13 h. Sixty per cent of the drug is metabolized by the liver into inactive metabolites. Forty per cent is excreted unchanged by the kidneys, with the majority of the hepatically metabolized product. In total, over 95% of the medication is excreted by the renal system.

Interactions
See Table 24.31.

Table 24.31 Interactions of lacosamide

Medications which alter lacosamide plasma levels	Medications whose plasma levels are altered by lacosamide
Levels decreased: phenobarbital and phenytoin	Levels decreased: oxcarbazepine (metabolite)

References

Chung S, Ben-Menachem E, Sperling MR, *et al*. Examining the clinical utility of lacosamide: pooled analyses of three phase II/III clinical trials. *CNS Drugs* 2010;24(12):1041–54.

Halász P, Kalviainen R, Mazurkiewicz-Beldzinska M, *et al*.; the SP755 Study Group. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. *Epilepsia* 2009;50(3):443–53.

Lamotrigine

Lamotrigine was first marketed in the UK as an ASM in 1991. It is a useful broad-spectrum ASM. It may be slightly less effective than carbamazepine in the treatment of focal-onset seizures but benefits from having fewer side effects. The commonest side effect is a rash, occurring in ~10% of patients. The incidence of rash is minimized by slowly titrating the dose to therapeutic levels.

Uses

Licensed uses

In the UK

- *Epilepsy*: lamotrigine is licensed for treatment as a monotherapy of focal-onset seizures and generalized seizures, including tonic–clonic seizures, in individuals aged 13 years and older. It is also licensed for the treatment of absence seizures in individuals aged 2 years and older. As an adjunct, it is licensed for the treatment of focal-onset seizures, generalized seizures, including tonic–clonic seizures and seizures associated with Lennox–Gastaut syndrome (LGS) in individuals aged 2 years and older.

In the USA

- *Epilepsy*: lamotrigine is licensed for treatment as a monotherapy for focal-onset seizures in individuals aged 16 years and older. Its use as a monotherapy is limited to second-line following conversion from one of the following ASMs: carbamazepine, phenobarbital, phenytoin, primidone, or valproate. As an adjunct, it is licensed for the treatment of focal-onset seizures, generalized seizures associated with LGS, and primary generalized tonic–clonic seizures in other epileptic syndromes in individuals aged 2 years and older.

Off-label uses

- Neuropathic pain, prophylaxis of SUNCT, prophylaxis of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) and trigeminal neuralgia.

Presentation

- *Trade names*: Lamictal® and Lamictal XR®. Generics are available.
- *Formulations*: lamotrigine is available as a dispersible, extended-release and a standard tablet. Dispersible tablet: 2 mg, 5 mg, 25 mg, and 100 mg. Standard tablet: 25 mg, 50 mg, 100 mg, 200 mg, and 250 mg. Extended-release tablet: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, and 300 mg.

Mechanism of action

The mechanism of action in epilepsy, neuropathic pain, and SUNCT is thought to be predominantly through blockade of voltage-gated sodium channels, thereby inhibiting neuronal depolarization and the transmission of both epileptic activity and nociceptive signals.

Toxicity and side effects

- Rash occurs in up to 10% of patients and will typically resolve with withdrawal of the medication. However, it cannot be predicted which rashes will progress to Stevens–Johnson syndrome. Serious rash occurs with an incidence of roughly 1/1000 in those >12 years old. The risk is increased with younger age, concomitant use of valproate, rapid initiation of medication, and when used in atopic individuals. Upon the development of a rash, lamotrigine should be immediately withdrawn unless the rash is clearly not drug related. The rash may also rarely represent the beginning of a multiorgan hypersensitivity syndrome.
- *Common—Dermatological*: rash (see above). It typically occurs in the first 8 weeks or if medication is suddenly stopped and resumed. *Gastrointestinal*: diarrhoea, dry mouth, nausea, and vomiting. *Musculoskeletal*: back pain. *Neurological*: dizziness, fatigue, headache, insomnia, and tremor. *Ophthalmological*: blurred and double vision. *Psychiatric*: aggression and irritability.
- *Serious—Dermatological*: Stevens–Johnson syndrome or toxic epidermal necrolysis. It is now thought that the risk of serious skin rash is comparable to other medications, such as carbamazepine and phenytoin, which have traditionally been seen as safer. *Gastrointestinal*: hepatic failure is very rare and usually, but not always, occurs within the context of a hypersensitivity reaction. *Haematological*: rarely, blood dyscrasias can occur, including anaemia, leucopenia, pancytopenia, and thrombocytopenia.

Contraindications

- *Absolute*: known hypersensitivity to lamotrigine or its excipients.
- *Relative*: lamotrigine may worsen myoclonic epilepsy. The dose should be reduced in hepatic dysfunction—50% of the dose should be used in moderate hepatic impairment, and 25% in severe hepatic impairment. Metabolites may also accumulate in renal failure; hence the maintenance dose should be reduced in severe renal impairment.

Use in special populations

- *Elderly*: elderly patients have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic interactions is higher.
- *Pregnancy*: animal studies have demonstrated some teratogenic side effects, but extensive experience in humans has not shown any increase in the risk of overall congenital malformation rates, risk of prematurity or miscarriage. Lamotrigine is a weak folate antagonist and hence expectant mothers should be prescribed high-dose folic acid. Use in pregnancy involves weighing up the potential benefits and side effects. Lamotrigine plasma concentrations will decrease markedly during pregnancy by up to two-thirds; hence an increase in dose may be required.
- *Lactation*: lamotrigine enters maternal milk, and breastfed infants can have plasma levels 25–50% of maternal plasma levels. Infants should be monitored for potential side effects, such as fatigue and irritability, and an alternative feeding regimen used if these are identified.

Efficacy

Epilepsy

- *Monotherapy in focal-onset seizures:* The 2007 SANAD study further supported the utility of lamotrigine in the treatment of focal epilepsy. In this unblinded study of 1,721 patients, for whom carbamazepine was determined to be standard of care, were randomized to one of five treatment arms: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate. Lamotrigine was found to be superior in extending time to treatment failure for all treatments except oxcarbazepine which it was equivalent to. Another arm of that study demonstrated inferiority of lamotrigine monotherapy in control of generalized seizures.
- *Adjunctive therapy in focal-onset seizures:* The efficacy of lamotrigine as an adjuvant agent in the treatment of focal seizures was established in a 1993 randomized double-blind study of 216 adults. Patients were randomized to have a 300 mg, 500 mg or placebo added to their anticonvulsant regimen. The patients were followed for 6 months. Patients on the highest dose of lamotrigine had a 36% reduction in seizure frequency compared to a 20% reduction with the 300 mg dose and an 8% reduction with the placebo.
- *Adjunctive therapy in primary generalized tonic–clonic (PGTC) seizures:* A 2005 double-blind placebo-controlled study of 117 patients aged

2–55 years established the efficacy of lamotrigine as an adjuvant in the treatment of PGTC seizures. After addition of lamotrigine (3–12 mg/kg/day for paediatric patients, 200–400 mg/day for adults) to their ASM regimen, patients experienced a 66% reduction in PGTC seizures compared to 34% in the placebo group.

SUNCT/SUNA

- A 2020 single-arm open-label study of 134 patients with SUNCT and SUNA demonstrated that 56% of patients experienced relief of symptoms at a mean dose of 314 mg/day. A meta-analysis included as part of the same study demonstrated similar efficacy of 59% responders for SUNCT and 56% for SUNA.
- For efficacy in neuropathic pain, see Chapter 5, Neuropathic pain.

Dosing and monitoring

Dosing

Titration of lamotrigine is performed slowly to reduce the incidence of side effects. If oral dosing is stopped for >5 days, then slow up-titration will need to be restarted.

- *Monotherapy of seizures*, age >12 years: start treatment with 25 mg od. After 2 weeks, increase to 50 mg/day in 1–2 divided doses; thereafter, lamotrigine can be increased by up to 100 mg/day every 1–2 weeks. The normal maintenance dosage is between 100 mg and 200 mg in 1–2 divided doses, although dosages up to 500 mg can be used.
- *Adjunctive therapy of seizures*, age >12 years: doses depend on whether it is used with valproate or enzyme-inducing drugs:
- *for adjunctive use with valproate*: start treatment at 25 mg on alternate days for 2 weeks, and then increase to 25 mg daily for 2 weeks. Then it can be increased by 50 mg/day every 1–2 weeks. The normal maintenance dose is 100–200 mg daily.
- *for adjunctive use without valproate but with enzyme-inducing drugs*: start treatment at 50 mg od for 14 days. Increase to 50 mg bd for a further 2 weeks, then increase by 100 mg/day every 1–2 weeks up to 700 mg daily. The normal maintenance dose is 200–400 mg/day in two divided doses.
- *for adjunctive use without valproate and without enzyme-inducing drugs*: start treatment at 25 mg od for 2 weeks. Increase to 50 mg/day in 1–2 divided doses for a further 2 weeks, then increase by a maximum of 100 mg every 1–2 weeks. The normal maintenance dose is 100–200 mg daily.
- *For SUNCT*: start treatment at 25 mg/day, then increase in 25 mg increments every 2 weeks. The final dose can range from 50 mg to 600 mg, depending on the response.

Monitoring

Hepatic and renal function should be assessed prior to starting and yearly while treatment is ongoing.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 3–15 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is >95% but can be reduced by food co-ingestion. T_{he} $_{\text{Tmax}}$ is 1–3 h, and plasma levels reach a steady state by 3–7 days. 90% of the lamotrigine dose is metabolized into inactive metabolites in the liver. Lamotrigine also undergoes autoinduction that may increase clearance by up to 37%, thus requiring an increase in dose. The half-life for lamotrigine varies dramatically, depending on whether valproate or enzyme inducers are co-prescribed. In the absence of both, the half-life is between 15 h and 35 h. With valproate, the half-life is 30–90 h; with enzyme inducers, it is 8–20 h, and, with both valproate and enzyme inducers, it is 15–35 h.

~100% of the medication is eliminated renally, 90% as inactive metabolites and the remaining 10% as unchanged drug.

Interactions

See Table 24.32.

Table 24.32 Interactions of lamotrigine

Medications which alter lamotrigine plasma levels	Medications whose plasma levels are altered by lamotrigine
Levels decreased: carbamazepine, eslicarbazepine acetate, methsuximide, olanzapine, oral contraceptives, oxcarbazepine, paracetamol, phenobarbital, phenytoin, primidone, retigabine, rifampicin, rufinamide, and ritonavir Levels increased: valproate	Levels decreased: clonazepam, levetiracetam, and valproate Levels increased: retigabine

References

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Marson AG, Al-Kharusi AM, Alwaidh M, *et al*. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369(9566):1000–15.

Marson AG, Al-Kharusi AM, Alwaidh M, *et al*; The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369(9566):1016–26.

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Motte J, Trevathan E, Arvidsson JF, *et al.* Lamotrigine for generalized seizures associated with the Lennox–Gastaut syndrome. Lamictal Lennox–Gastaut Study Group. *NEJM* 1997;337(25):1807–12.

Pareja J, Alvarez M, Montojo T. SUNCT and SUNA: recognition and treatment. *Curr Treat Options Neurol* 2013;15(1):28–39.

Steinhoff BJ, Ueberall MA, Siemes H, *et al*.; LAM-SAFE Study Group. The LAM-SAFE Study: lamotrigine versus carbamazepine or valproic acid in newly diagnosed focal and generalized epilepsies in adolescents and adults. *Seizure* 2005;14(8):597–605.

Lasmiditan

Lasmiditan is a first-in-class, selective 5-HT$_{1F}$ agonist licensed for treatment of acute migraine. The FDA approved it for use in 2019. A recent meta-analysis has concluded that lasmiditan may have a lower odds ratio of being pain-free at 2 h when compared to triptans, but a similar OR when compared to gepants. The same meta-analysis concluded lasmiditan was associated with a higher rate of adverse events than gepants or triptans. Its main advantage over triptans is that it is safe to use in individuals with cardiovascular disease.

Uses

Licensed uses

In the USA (lasmiditan is not licensed for use in the UK)

- *Migraine:* Lasmiditan is licensed for the acute treatment of migraine in individuals aged 18 years and older.

Off-label uses

- None

Presentation

- *Trade names*: Reyvow®. Generics are not available.
- *Formulations*: lasmiditan is available as a 50 mg and 100 mg tablet.

Mechanism of action

Lasmiditan is a 5-HT$_{1F}$ agonist. Its exact mechanism of action in the management of migraine is unclear. It is likely that, its clinical effects are at least in part mediated by a reduction in CGRP release from the trigeminovascular system and by inhibiting glutamatergic neurons, implicated in central pain pathways.

Toxicity and side effects

- *Common*—Cardiovascular: Reduction in heart rate by 5–10 bpm and increase in diastolic and systolic blood pressure by 2–3 mmHg. *Gastrointestinal*: nausea, vomiting. *Neurological*: dizziness, fatigue, muscle weakness, paraesthesia, and sedation.
- *Serious— Immunological:* Hypersensitivity reactions, including angioedema.

Contraindications

- *Absolute*: Hypersensitivity to lasmiditan or its excipients. Use is not recommended in severe hepatic impairment.
- *Relative*: No dose reductions are required in mild or moderate hepatic impairment, or in any degree of renal impairment.

Use in special populations

- *Elderly*: consider reduced doses in the elderly and monitor for significant elevations in blood pressure. Individuals aged 65 and older were associated with higher rates of adverse events and a larger increase in systolic blood pressure than younger participants in the clinical trials.
- *Pregnancy*: Some animal studies have demonstrated teratogenic effects at exposure levels equivalent to 10 times the maximum recommended human dose; however, there is no date from use in humans. Use only if the potential benefits outweigh the potential risks.
- *Lactation*: There is no data on the presence of lasmiditan in human milk, although animal studies have demonstrated it is present in rodent milk at 3 times the level present in maternal plasma. If nursing mothers use it, infants should be monitored for potential side effects and an alternative treatment or method of feeding should be used if side effects are identified.

Efficacy

The CENTURION trial was a phase 3, randomized, placebo-controlled trial, which evaluated the efficacy of lasmiditan in the acute treatment of migraine. Patients treated with lasmiditan demonstrated statistically significant higher rates of pain freedom at 2 h of 29.3% with 200 mg lasmiditan and 25.8% with 100 mg lasmiditan, compared to 8.4% with placebo ($p < 0.001$ for both doses).

Dosing and monitoring

Dosing

Take 50, 100, or 200 mg at the start of a migraine. A second dose is unlikely to provide any added clinical benefit.

Monitoring

No routine monitoring is required. Consider monitoring heart rate in patients at risk of significant bradycardia.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is approximately 40%. Median T_{max} is 1.8 h; this is delayed by 1 h if taken with a high-fat meal. Lasmiditan is 55–60% protein-bound. Lasmiditan undergoes both hepatic and extra-hepatic metabolism. CYP enzymes have a minimal role in its metabolism. Metabolites are inactive and are predominantly excreted by the renal system. The mean half-life in young men is 5.7 h.

Interactions

See Table 24.33.

Table 24.33 Interactions of lasmiditan

Medications whose plasma levels are altered by lasmiditan	Pharmacodynamic interactions
Levels increased: P-gp or BRCP substrates e.g. digoxin, indinavir, ritonavir, and verapamil.	With CNS depressants, e.g. alcohol: may increase the risk of confusion and sedation. With heart rate lowering drugs: Increased risk of bradycardia. With serotonergic drugs: Increased risk of serotonergic syndrome.

References

Ashina M, Reuter U, Smith T, *et al*. Randomised, controlled trial of lasmiditan over four migraine attacks: findings from the CENTURION study. *Cephalalgia* 2021;41(3):294–304.

Yang C, Liang C, Chang C, *et al*. Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. *JAMA Netw Open* 2021;4(10):e2128544.

Levodopa

Levodopa was first used as an oral agent in the treatment of PD in 1967. It is the most effective medical treatment for PD, but long-term use is often complicated by motor fluctuations and dyskinesias.

Uses

Licensed uses

In the UK/USA

- *Parkinson's disease*: used for the treatment of PD at any stage of the disease process as monotherapy or in combination with other antiparkinsonian agents, in individuals aged 18 years and older. Several directly delivered enteral suspensions (Duodopa® and Lecigon® available in the UK and Duopa® in the US) are licensed for the treatment of advanced levodopa-responsive PD with severe motor fluctuations and dyskinesia if the effects of other levodopa formulations are not sufficient.

In the USA

- *Parkinson's disease*: An inhaled formulation (Inbrija®) is available for the treatment of OFF periods in patients with PD.

Off-label uses

- Dystonia, Parkinson's plus syndromes, and RLS.

Presentation

Levodopa is available as a combination therapy with a dopa decarboxylase inhibitor (DDI); benserazide (co-beneldopa) or carbidopa (co-careldopa). It is also available as a gel co-formulated with carbidopa for use with an enteral infusion pump (Duodopa® in the UK and Duopa® in the US) for the management of advanced disease. Levodopa/carbidopa is available co-formulated with entacapone, both as an oral tablet (Stalevo®/Stanek®), and as a gel for continuous jejunal infusion (Lecigon®)

Co-beneldopa

- *Trade names*: Madopar® and modified-release Madopar® CR. Generics are available.
- *Formulations*: co-beneldopa (benserazide/levodopa) is available as a dispersible tablet, a modified-release capsule and tablet, as well as a standard tablet. Dispersible tablet: 12.5/50 mg and 25/100 mg. Modified-release capsule: 12.5/50 mg, 25/100 mg, and 50/200 mg. Modified-release tablet: 25/100 mg. Standard tablet: 12.5/50 mg, 25/100 mg, and 50/200 mg.

Co-careldopa (oral)

- *Trade names*: Parcopa®, Sinemet®, Apodespan®, Lecado®, Rytary®, and modified-release Caramet® CR. Stalevo® /Stanek® is co-formulated with entacapone. Generics are available.
- *Formulations*: co-careldopa (carbidopa/levodopa) is available as a modified-release tablet and a standard tablet. Modified-release tablet: 25/100 mg and 50/200 mg. Standard tablet: 12.5 mg/50 mg, 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg. Co-formulation with entacapone (carbidopa/levodopa/entacapone): 12.5/50/200 mg, 18.75/75/200 mg, 25/100/200 mg, 31.25/125/200 mg, 37.5/150/200 mg, and 50/200/200 mg.

Co-careldopa (enteral)

- *Trade names*: Duodopa® and Duopa®. Generics are not available. Lecigon® is co-formulated with entacapone.
- *Formulations*: available as gel for enteral infusion: Duodopa®/Duopa®: 5 mg(carbidopa)/20 mg(levodopa)/mL in a 100 mL cassette. Lecigon®:one 47 mL cartridge contains 940 mg levodopa, 940 mg entacapone and 235 mg carbidopa, i.e. 20 mg/mL levodopa, 20 mg/mL entacapone and 5 mg/mL carbidopa.

Levodopa (inhaled)

- *Trade names*: Inbrija®. Generics are not available. Inbrija® does not contain carbidopa or benserazide but is only licensed for us in patients already on oral levodopa therapies.
- *Formulations*: Inbrija® is available as a capsule for inhalation. The capsule contains 42 mg of dry powder formulation levodopa.

Mechanism of action

PD is characterized by destruction of dopaminergic neurons within the substantia nigra of the midbrain. Levodopa crosses the blood–brain barrier to be converted to dopamine. Levodopa is always used in conjunction with a DDI (carbidopa or benserazide). DDIs do not cross the blood–brain barrier, but act to prevent the peripheral conversion of levodopa to dopamine. This results in greater concentration of levodopa reaching the brain, as well as reduces side effects that result from peripherally acting dopamine (nausea and vomiting). Similarly, levodopa can be administered in a combined formulation with an inhibitor of COMT, such as entacapone to prevent degradation to the inactive 3-O-methyldopa metabolite (see COMTIs p. 376).

Toxicity and side effects

- *Common—Cardiovascular*: postural hypotension. *Gastrointestinal*: anorexia, nausea, and vomiting. *Neurological*: dyskinesias (60% of patients after long-term therapy. This appears to be dependent on the dose, duration, and onset age, with younger patients usually affected sooner). On–off phenomenon (periods of akinesia and improved mobility with dyskinesias) after prolonged therapy. *Psychiatric*: agitation, anxiety, confusion, depression, hallucinations, insomnia, and somnolence.
- *Serious—Cardiovascular*: arrhythmias (rare), e.g. ventricular extrasystoles and AF. *Dermatological:* epidemiological studies have demonstrated an elevated prevalence of melanoma (2–6 times higher) in patients with PD. It is unclear if this is due to medication or the underlying disease but is considered more likely to be due to the disease. *Neurological*: sudden-onset sleep.
- In addition to the above potential side effects, the inhaled form of levodopa (Inbrija®) led to cough, discoloured sputum, and respiratory tract infections at a higher rate than placebo.

Contraindications

- *Absolute*: angle-closure glaucoma, severe psychosis or deterioration in psychiatric illness after commencement, and patients using non-selective MAOIs. Inbrija® can cause bronchospasm. It should be avoided in asthma, COPD, and chronic lung disease.
- *Relative*: no dose alteration is required in hepatic or renal impairment.

Use in special populations

- *Elderly*: levodopa is considered safe for the elderly; no dose adjustment is required.
- *Pregnancy*: teratogenicity was noted in animal studies. There is limited data on the use of levodopa preparations in pregnancy. A recent review suggested that out of 148 published pregnancies, no increased risk of spontaneous abortions or congenital malformations was identified when compared to general population levels. Use in pregnancy if benefits outweigh risks.
- *Lactation*: levodopa is excreted into breast milk in small quantities, best estimates suggest the infant dose would be <0.5% of the maternal dose. There is limited published information but there have been no significant reports of harm to infants if their mothers have taken levodopa preparations whilst nursing. Levodopa preparations may reduce maternal prolactin levels, although this may not impair her ability to breastfeed.

Efficacy

- *Parkinson's disease:* The efficacy of levodopa/DDI in the treatment of PD has been known since 1961. It remains the gold standard of treatment. The 2004 *ELLDOPA* (Early versus Late Levodopa in PD) study was a double-blind RCT designed to assess long-term effects of levodopa/carbidopa. It assigned patients with untreated PD (*n* = 361) to a daily dose of either 150 mg, 300 mg, or 600 mg of levodopa or placebo for 40 weeks with a 2-week withdrawal period. Patients treated with levodopa demonstrated a significant improvement in their Unified Parkinson's Disease Rating Scale (UPDRS) scores, compared to placebo, and higher doses were associated with an increased risk of dyskinesia.

- *Restless legs syndrome:* A 2011 Cochrane systematic review and meta-analysis reviewed 6 placebo-controlled and 3 active-controlled studies of the efficacy of levodopa/carbidopa in the treatment of RLS across 521 patients. Two studies reported symptom severity (0–10). For these studies, the pooled mean difference was –1.34 (p = 0.002) favouring treatment with levodopa/carbidopa over placebo. Periodic limb movement improved by –26.28 (p <0.0001) in those treated with levodopa/carbidopa over placebo. Two studies demonstrated superiority of dopamine agonists (cabergoline and pramipexole) with regards to IRLS score compared to levodopa/carbidopa. Thus, dopamine agonist therapy may be preferred if patients can tolerate it.

Dosing and monitoring

Dosing

1. PD.

- For oral treatments start treatment at 50–100 mg of levodopa bd to tds. This can be increased by 100 mg of levodopa daily to a usual maintenance dose of 100 mg of levodopa tds. If response is insufficient, doses of 1000 mg or more daily (if tolerated) should be considered, with some experts advocating up to 2000–3000 mg. However, the aim is to use the lowest effective dose. Nausea and vomiting experienced by many patients commenced on levodopa may be treated with domperidone (20 mg bd to tds), for as short a time as possible due to concern of cardiac side effects.
- For inhaled formulations: (Inbrija®) inhale 2 capsules (84 mg) up to 5 times a day.
- For infusion-based treatments: Duodopa® and Lecigon® are used where other treatments have failed or with severe motor fluctuations. Duodopa®: The manufacturer advises a morning bolus equivalent to the patient's usual morning levodopa dose infused over 10–30 min. This is followed by a maintenance infusion of the patient's daily levodopa dose over 16 h. Bolus doses (0.5–2 mL) are used for periods of hypokinesia. If >5 boluses are needed, the maintenance dose should be increased. Lecigon®: As Lecigon® contains entacapone, it may be necessary to reduce the total dose of levodopa on cross-titration of oral levodopa therapies by ~30%. The maximum daily dose is 100 mL (2000 mg levodopa), the maintenance dose is usually 0.7–5 mL/h corresponding to 15–100 mg levodopa/h, usually given over 16 h. The maintenance dose is typically increased in increments of 2 mg (0.1 mL)/h. A morning and extra bolus dose can also be given 5–10 mL (100–200 mg levodopa) for the morning dose and typically <3 mL for the bolus (60 mg levodopa).

- Gradual dose reduction is advised when treatment is being discontinued, in order to avoid NMS. Where patients are temporarily unable to take oral medication (e.g. preoperatively), an alternative route of dopamine administration should be used (e.g. DA by transdermal patch).

2. RLS.

- Immediate-release tablet: 12.5/50–25/100 mg (0.5–1 tablet) given in the evening, at bedtime, or upon waking during the night with RLS symptoms.
- Controlled-release tablet: 25/100 mg (one tablet) before bedtime for RLS symptoms that awaken the patient during the night.

Monitoring

Monitor for the onset of motor complications in PD and augmentation in RLS.

Pharmacokinetics and interactions

Pharmacokinetics

There is significant inter-person variability in the absorption of levodopa. Oral bioavailability of levodopa is 98% (extended-release 75%, inhaled 70%). T_{max} is 1–2 h (inhaled 0.5 h). Increased protein intake lowers absorption across the gut and movement across the blood–brain barrier. Administration with a peripheral DDI increases the amount of levodopa crossing the blood–brain barrier from 1–3% to 10%. Levodopa and DDIs are 10–30% protein-bound. Levodopa is metabolized primarily through decarboxylation by aromatic amino acid decarboxylase. This is present in a range of peripheral tissues, including the intestine, kidneys, liver, and spleen, as well as the brain. This produces dopamine which is metabolized further to 3,4-dihydroxyphenylacetic acid (DOPAC) and subsequently to inactive homovanillic acid (HVA). The half-life of levodopa is 1.5 h when administered with a DDI. Eighty per cent of the dose is excreted renally as its metabolites (DOPAC and HVA).

The pharmacokinetic profile of infused formulations is similar to that of other preparations. However, the morning bolus allows for therapeutic concentrations to be reached in 10–30 min, and there is significantly less fluctuation in plasma concentrations (and hence theoretically a reduction in the occurrence of motor fluctuations, when compared to traditional oral preparations). The half-life of levodopa with entacapone in Lecigon® is 2 h.

Interactions

See Table 24.34.

Table 24.34 Interactions of levodopa

Medications which alter levodopa plasma levels	Pharmacodynamic interactions
Levels decreased: anticholinergics, pyridoxine, and TCAs.	With non-selective MAOIs: may cause hypertensive crises.
Levels increased: antacids	With antihypertensives: may cause orthostatic hypotension

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Lidocaine

In the context of neurology, lidocaine is most commonly used as a patch in the management of post-herpetic neuralgia. Off-label, lidocaine has also been used since the 1980s as an adjunct in the treatment of cluster headache and acute episodes of SUNCT. The effects of lidocaine on cluster headache are modest, and it is best used when patients have not responded to more conventional agents.

Uses

Licensed uses

In the UK/USA

- *Post-herpetic neuralgia*: lidocaine patches are licensed topically for post-herpetic neuralgia in individuals aged 18 years and older.

Off-label uses

- Allodynia (patch), cluster headache (intranasal) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing SUNCT (IV).

Presentation

- *Trade names*: Laryngojet®, Lidoderm®, LTA 360 Kit®, Versatis®, and Xylocaine®. Generics are available.
- *Formulations*: lidocaine is available in a number of different formulations. In neurology, it is used in the management of cluster headache as an intranasal spray, in post-herpetic neuralgia as a patch, and in SUNCT as an IV infusion. Intranasal spray: lidocaine 4% (4 mg/mL) and lidocaine 10% (10 mg/mL) concentrations in 4 mL and 50 mL bottles, respectively. IV infusion: 1% and 2% w/v in 2 mL, 5 mL, 10 mL, and 20 mL ampoules. Patch: 5% w/w lidocaine.

Mechanism of action

Lidocaine acts by blocking neuronal voltage-gated sodium channels, hence reducing neuronal activation. The effect of lidocaine on trigeminal autonomic cephalalgias (TACs) is thought to be via inhibition of neuronal activation in the sphenopalatine ganglion, an area believed to be involved in the pathogenesis of cluster headache. In post-herpetic neuralgia, it is believed to act locally by reducing the activity of nociceptive neurons.

Toxicity and side effects

In the doses used for cluster headache and post-herpetic neuralgia, side effects are few, typically localized, and, unlike when used as an IV infusion, systemic toxicity is uncommon.

- *Common—Cardiac*: hypotension. *Dermatological*: erythema, local irritation, oedema, petechiae. *Gastrointestinal*: nausea and vomiting. *Neurological*: confusion, drowsiness, headache, paraesthesiae.
- *Serious—Cardiac*: arrhythmias, bradycardia, cardiorespiratory arrest. *Haematological*: methaemoglobinaemia. *Immunological*: anaphylaxis. *Neurological*: coma, convulsions, malignant hyperthermia.

Contraindications

- *Absolute*: acute porphyria, congestive heart failure, previous hypersensitivity, second- and third-degree heart block with no pacemaker, sinoatrial disease, Wolff–Parkinson–White syndrome.
- *Relative*: use with caution in hepatic and renal impairment, due to increased risk of adverse effects. Dose adjustment is not usually required.

Use in special populations

- *Elderly*: the lidocaine patch is usually well tolerated in elderly patients; however, the intravenous formulation should be used only with significant caution as they are more prone to toxicity due to an age-related decline in renal and hepatic function and are more likely to suffer from cardiac disease.
- *Pregnancy*: lidocaine has not been shown to be harmful during pregnancy in animal studies, and there are no confirmed reports of teratogenicity in humans. It should only be used if the benefits outweigh the risks.
- *Lactation*: lidocaine is present in breast milk, but the amount is considered too small to be harmful.

Efficacy

- *Neuropathic pain*: a systematic review found three studies, involving 314 patients with post-herpetic neuralgia treated with topical lidocaine. All studies found a beneficial effect, and a meta-analysis of two of the studies found a statistically significant effect for lidocaine vs. placebo for secondary outcome measures (mean improvement in pain scores of 0.42 on a 10-point scale, 95% CI 0.14–0.69; $p = 0.003$). The authors concluded that there is still insufficient evidence to recommend topical lidocaine as the first line in the treatment of any neuropathic pain syndrome. NICE guidance agrees with this conclusion and only recommends topical lidocaine in the treatment of localized neuropathic pain in patients unable to tolerate or use oral medications. Notably, the EFNS recommends topical lidocaine as first-line treatment for post-herpetic neuralgia in elderly patients.
- *TACs*: there is limited data on the efficacy of intranasal lidocaine in aborting cluster headache attacks. One open-label study of 30 male

patients with cluster headache who were given 4% lidocaine intranasally found that 54% experienced some relief. The only RCT of intranasal lidocaine looked at nine patients with cluster-like headaches induced with glyceryl trinitrate and subsequently treated with intranasal cotton wool swabs soaked in either 10% cocaine hydrochloride, 10% lidocaine, or saline. Patients were pain-free with cocaine after 31.3 ± 13.1 min, and with lidocaine after 37.0 ± 7.8 min. With placebo, there was an increase in headache severity after application, and time to recovery was 59.3 ± 12.3 min. IV lidocaine has been shown in case reports to have some efficacy in the termination of SUNCT attacks. Freedom from attacks may only be maintained for the duration of the infusion.

Dosing and monitoring

Dosing

- *Cluster headache*: the dose advised is 1 mL of lidocaine (4–10%) in the ipsilateral nostril, given as a spray or as a drop. Repeat dosing should be avoided.
- *Post-herpetic neuralgia*: apply patches, as required, to the affected area for a maximum of 12 h each day. Assess whether there has been benefit from treatment after a minimum of 2 weeks.
- *SUNCT*: a loading dose of 1 mg/kg can be given (optional). The maintenance dose is 1–4 mg/kg/h IV, given for a maximum of 7 days.

Monitoring

Monitoring is not needed for the nasal spray or topical patch. Patients should have an ECG done and liver and renal function checked before starting the infusion. Continuous cardiac monitoring and regular BP monitoring should be in place during infusions.

Pharmacokinetics and interactions

Pharmacokinetics

Lidocaine is absorbed rapidly and extensively when given topically. The rate and extent of absorption are variable, depending on the concentration, site of application, and length of exposure. It undergoes extensive first-pass metabolism by the liver where it is de-ethylated to form the active metabolites monoethylglycinexylidide and glycinexylidide. These metabolites have a half-life of 2 h and 10 h, respectively, and, although active, they are less potent than lidocaine, which has a half-life of 1.5–2 h. 60–80% of the drug is protein-bound. Metabolism is predominantly hepatic. Less than 10% of unchanged lidocaine is excreted by the kidneys.

Interactions

See Table 24.35.

Table 24.35 Interactions of lidocaine

Medications which alter lidocaine plasma levels	Pharmacodynamic interactions
Levels increased: cimetidine and protease inhibitors	With agents causing hypokalaemia: reduced efficacy of lidocaine with hypokalaemia. With antiarrhythmics: increased risk of arrhythmias With antipsychotics: risk of prolonged QT With β-blockers and other local anaesthetics: can cause myocardial depression

References

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Lomustine

Lomustine was first licensed in the 1970s for the treatment of brain tumours. It is one of a class of alkylating agents called nitrosoureas. It benefits from being markedly lipophilic, allowing rapid diffusion across the blood–brain barrier. Its main limitations are a delayed myelosuppressive effect and a cumulative toxic effect on renal and pulmonary function. It is either used as a monotherapy, or in combination with procarbazine and vincristine (PCV) for the treatment of recurrent high-grade glioma.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Brain tumours*: lomustine is licensed for use in the management of both primary and metastatic brain tumours, usually in combination with radiotherapy ± surgery, in individuals of all ages.

Off-label uses

- None.

Presentation

- *Trade names*: Gleostine®, CCNU®. Generics are available.
- *Formulations*: lomustine is available as a 10 mg, 40 mg, and 100 mg capsules (only available as 40 mg in the UK).

Mechanism of action

Lomustine is a cell cycle nonspecific alkylating agent that acts by forming cross-links in both DNA and RNA. This inhibits DNA and protein synthesis. Part of its action may also be mediated by carbamoylation of amino acids.

Lomustine is highly lipid-soluble at physiological pH, allowing it to rapidly distribute across the blood–brain barrier.

Toxicity and side effects

The most common adverse effect is myelosuppression. This is often delayed, and dose-related. Thrombocytopenia occurs at 4 weeks and lasts 1–2 weeks. Leucopenia <5000 white blood cells (WBCs)/mm^3 occurs in 65% at 5–6 weeks. Anaemia is less common and less severe.

- *Common—Gastrointestinal*: anorexia, nausea, and vomiting.
- *Serious—Haematological*: acute leukaemia, bone marrow failure, and bone marrow dysplasia. *Ophthalmological*: irreversible visual loss can rarely occur if used with radiation. *Renal*: progressive renal failure has been reported in patients with high cumulative doses; hence the maximum recommended lifetime total dose is 1000 mg/m^2. *Respiratory*: interstitial pneumonia and lung fibrosis (delayed onset has been reported up to 6 months with lomustine, and up to 17 years post-treatment with other nitrosoureas).

Contraindications

- *Absolute*: previous hypersensitivity to nitrosoureas, coeliac disease, severe bone marrow depression, and severe renal impairment.
- *Relative*: reduced pulmonary function at baseline. Men should be warned about the possibility of permanent infertility. Lomustine is hepatically metabolized; hence caution should be used in hepatic impairment.

Use in special populations

- *Elderly*: no clinical studies have looked directly at the use of lomustine in those over 65 years old. The elderly have an age-related deterioration in their renal and hepatic function, and benefit from lower dosing regimens.
- *Pregnancy*: lomustine is teratogenic and embryotoxic in animal studies. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant.
- *Lactation*: lomustine levels within breast milk is unknown. The drug is lipophilic and hence is likely to transfer to the newborn in this manner. Mothers should be given advice about the benefits of breastfeeding vs. the potential adverse effects of the drug and offered alternative methods of feeding.

Efficacy

Lomustine is commonly used in combination with procarbazine and vincristine, as part of procarbazine, lomustine, and vincristine (PCV) chemotherapy in the treatment of gliomas. A meta-analysis of 18 studies conducted in 1993 estimated that combined radiation and chemotherapy was associated with an increased survival of 10.1% at 1 year and 8.6% at 2 years, compared to radiotherapy alone for patients diagnosed with malignant glioma. In contrast, a large RCT looking at the same question showed no significant difference in median survival between radiotherapy and radiotherapy with PCV (9.5 vs. 10 months, respectively). Response rates for nitrosourea-based chemotherapy for the management of recurrent anaplastic astrocytoma and glioblastoma multiforme vary but are estimated to range between 8% and 27%.

Dosing and monitoring

Dosing

The dosage of lomustine varies, depending on the body surface area (BSA), bone marrow status, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines.

For use as a single agent in treatment-naïve patients without bone marrow depression, the initial dose is typically 120–130 mg/m^2. Patients usually receive a single oral dose every 6–8 weeks. The dose is then adjusted, based on haematological parameters. No dose adjustment is needed of nadir leukocytes after prior dose >3000/mm^3 and platelets >75 000/mm^3. If nadir leukocytes are 2000–3000/mm^3 and nadir platelets >25 000/mm^3 dose should be reduced by 30%. If nadir platelets are 25 000–74 999/mm^3 and nadir leukocytes >2000/mm^3 dose should also be reduced by 30%. Lastly, if either nadir leukocytes <2000/mm^3 or if nadir platelets <25 000/mm^3 the dose should be reduced by 50%.

Monitoring

Prior to initiation of treatment, FBC, renal, liver, and pulmonary function should be assessed. An FBC is recommended once weekly for at least 6 weeks post-dose. Liver, pulmonary, and renal function should be assessed regularly during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of lomustine is difficult to assess, as it rapidly decomposes in the gastrointestinal tract, with no intact drug detectable in the plasma, following oral administration. Lomustine decomposes to multiple metabolites, including cyclohexylamine, cyclohexylisocyanate, and N,N′-dicyclohexylurea. The relative pharmacological activity of these metabolites is unknown. T_{max} occurs at 3 h. The metabolites are highly lipophilic, allowing rapid diffusion across the blood–brain barrier. CSF levels are 30% plasma levels. The half-life of metabolites is variable and ranges from 4 h to 72 h. The details of further metabolism of lomustine metabolites are unknown. In trials using radiolabelling, 50% of radioactivity is excreted in the urine by 24 h, with the majority of the rest excreted by 72 h and <5% excreted in faeces.

Interactions

See Table 24.36.

Table 24.36 Interactions of lomustine

Medications which alter lomustine plasma levels	Pharmacodynamic interactions
Levels decreased: phenobarbital	With other chemotherapeutic agents, cimetidine, clozapine, and theophylline: may increase severity of myelosuppression

References

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Low-molecular-weight heparin, e.g. tinzaparin

Tinzaparin was first marketed in the UK in 1993 and is one of numerous preparations of low-molecular-weight heparin (LMWH) used globally. Other commonly used preparations include dalteparin, enoxaparin, and nadroparin.

Uses

Licensed uses

In the UK/USA

- LMWHs are licensed for the treatment of deep vein thrombosis with or without pulmonary embolism in individuals aged 18 years and older.

Off-label uses

- Cerebral venous sinus thrombosis.

Presentation

- *Trade names*: Innohep®. Generic forms are not available.
- *Formulations*: tinzaparin is available as 10,000 iu/mL and 20,000 iu/mL pre-filled syringes.

Mechanism of action

Tinzaparin is an antithrombotic agent. It potentiates the inhibition of several activated coagulation factors, especially factor Xa and IIa. Primary inhibitory activity is mediated through the plasma protease inhibitor, antithrombin III.

Toxicity and side effects

See Unfractionated heparin, p. 733.

Contraindications

See Unfractionated heparin, p. 733.

Use in special populations

See Unfractionated heparin, p. 733.

- *Elderly*: no dose reduction required; however, the elderly experience an age-related impairment in renal function; hence regular monitoring of renal function is recommended.
- *Pregnancy:* No dosing adjustment is required. Tinzaparin is not predicted to increase the risk of developmental abnormalities.
- *Lactation:* Tinzaparin and other LMWHs are not present in breast milk in clinically relevant amounts. They are safe to use by nursing mothers.

Efficacy

- *Cerebral venous sinus thrombosis*: a Cochrane review conducted by Coutinho *et al*. in 2012 highlighted the paucity of evidence regarding the use of anticoagulation in cerebral venous sinus thrombosis. It highlighted that several small RCTs have shown that early anticoagulation is effective, and thus obtaining ethical approval for larger, more robust studies has not been considered appropriate. Based upon the limited evidence available, anticoagulant treatment for cerebral venous sinus thrombosis is both safe and associated with a potentially important (although not statistically significant) reduction in the risk of mortality and neurological morbidity. Limited data suggest that LMWH is more effective than unfractionated heparin and at least as safe for the treatment of cerebral venous sinus thrombosis. LMWH may also be preferred due to ease of monitoring.

Dosing and monitoring

Dosing

For the treatment of cerebral venous sinus thrombosis, the LMWH should be administered at treatment dose. For tinzaparin, this is 175 units/kg od.

Monitoring

Platelet counts should be measured in patients before the start of treatment and periodically thereafter. Treatment should be stopped immediately in those who develop thrombocytopenia.

Reversal

In cases of overdose, protamine sulfate (1%) via slow IV infusion can be given at a dose of 1 mg protamine for every 100 anti-Xa IU given. If the aPTT remains prolonged after 2–4 h, a second infusion of 0.5 mg per anti-Xa can be given. Extreme care should be taken when giving protamine sulfate to prevent overdosage.

Pharmacokinetics and interactions

Pharmacokinetics

Tinzaparin has a bioavailability of around 90%, following a SC injection. The absorption half-life is 200 min, with peak plasma activity being observed after 4–5 h. The elimination half-life is about 90 min. Tinzaparin is primarily renally excreted.

Interactions See Unfractionated heparin, p. 733.

References

Coutinho J, De Brujin S, DeVeber G, *et al.* Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev* 2011(8):CD002005.

Melatonin

Melatonin standard and modified-release formulations have variable licensing status worldwide. In the USA, they are termed a dietary supplement, while, in the UK, use requires a prescription. A melatonin prolonged-release formulation Circadin® was first marketed in the UK in 2008. It is indicated primarily for the treatment of primary insomnia in those over 55-years-old, although off licence uses have seen it trialled in a variety of sleep disorders. It has modest efficacy in the treatment of primary insomnia and a relatively benign side effect profile.

Uses

Licensed uses

In the UK

- *Insomnia*: a melatonin prolonged-release formulation (Circadin®) is licensed for use as monotherapy in the short-term treatment of primary insomnia typified by poor-quality sleep in patients aged 55 years and older.
- *Jet lag*: Ceyesto® is a recently approved 3 mg immediate release tablet indicated for jet lag.

In the USA

Melatonin is regulated through the FDA's Dietary Health and Education Act as a 'dietary supplement'; hence it can be purchased by individuals of any age and does not require a prescription.

Off-label uses

- Circadian rhythm sleep disorders and REM sleep behaviour disorder (RBD).

Presentation

- *Trade names*: Ceyesto® and Circadin®. Generics are available.
- *Formulations*: melatonin prolonged release is available as a 2 mg tablet. Melatonin immediate-release is available as a 3 mg tablet.

Mechanism of action

Melatonin is an endogenous hormone which acts on melatonin receptors 1–3. It is secreted by the pineal gland during darkness, peaking at 2–4 a.m. It is believed to regulate the body's circadian rhythm. There is an age-related decline in melatonin secretion. Hence it is believed that, in those >55 years old, exogenous melatonin tops up endogenous levels, preventing primary insomnia.

Toxicity and side effects

Melatonin is a relatively safe drug; side effects are uncommon. In clinical trials, the most common side effects were arthralgia, back pain, headache, nausea, and nasopharyngitis. These were seen at similar levels in placebo groups.

- *Serious—Dermatological*: cases of angio-oedema have been reported.

Contraindications

- *Absolute*: hypersensitivity to melatonin and lactose intolerance.
- *Relative*: no data are available with regard to use in hepatic or renal impairment; hence the manufacturer advises against use in hepatic impairment (the latter due to the fact that clearance will be markedly reduced in these individuals) and advises caution if used in renal impairment.

Use in special populations

- *Elderly*: melatonin is primarily indicated for the elderly population. Melatonin bioavailability and metabolism reduce with age.
- *Pregnancy*: animal studies have not demonstrated harmful effects in pregnancy. However, there are no clinical data with regard to melatonin use in human pregnancies; hence the manufacturer recommends avoidance in pregnancy.
- *Lactation*: as endogenous melatonin is present in human breast milk, exogenous melatonin is also likely to be present. There are no studies exploring the effects of increased melatonin levels on the infant, it is unlikely to cause significant harm, but due to the lack of data the manufacturers have stated that it cannot recommend its use in breastfeeding mothers.

Efficacy

A number of RCTs have looked at the use of prolonged-release melatonin in the treatment of primary insomnia in >55 year olds. One of the latest studies published in 2009 demonstrated that 50% of individuals treated with prolonged-release melatonin had substantial improvement in sleep quality vs. 15% with placebo.

Melatonin has been studied in the context of RBD, however the results are conflicting. A recent, small 12-week randomized placebo-controlled study of 30 patients with RBD failed to show a significant effect of Circadin 4 mg on overnight RBD sleep events as captured by patient diary. Several older studies suggested benefits when polysomnography-based outcomes, such as REM sleep epochs, were taken into account at similar doses.

Dosing and monitoring

Dosing

Start treatment at 2 mg od ~1 h prior to sleep and after food. This can be used for up to 13 weeks. No rebound effects have been identified on stopping treatment. Doses of 2–12 mg are required for RBD.

Monitoring

No monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics

The exact bioavailability of melatonin from Circadin® is unknown. In other oral formulations of melatonin, it is ~15% due to substantial first-pass metabolism. This figure is halved in the elderly. Peak plasma concentration occurs at 1.6 h. Co-digestion with food delays this by 1 h. Melatonin is 60% protein-bound. The half-life of Circadin® is 3.5–4 h. It is predominantly metabolized hepatically by CYP1A1–2, and potentially CYP2C19, enzymes, into sulphated and glucuronide conjugates. The predominant metabolite, a sulphated conjugate, is inactive. Metabolites are excreted by the renal tract within 12 h of ingestion; <2% is excreted as unchanged melatonin. There is a 3–4× increase in C_{max} in women compared to men, but no pharmacodynamic differences were found despite the difference in blood levels.

Interactions

See Table 24.37.

Table 24.37 Interactions of melatonin

Medications which alter melatonin plasma levels	Medications whose plasma levels are altered by melatonin	Pharmacodynamic interactions
Levels decreased: CYP1A2 inducers, e.g. carbamazepine, nicotine, and rifampicin Levels increased: CYP1A2 inhibitors, e.g. cimetidine, fluvoxamine, and oestrogen-containing compounds	Levels decreased: melatonin induces CYP3A *in vitro*; hence plasma concentrations of other medications metabolized by this enzyme may fall	With alcohol: reduced impact of Circadin® on sleep With hypnotics, e.g. benzodiazepines, and Z-drugs, e.g. zopiclone: increased sedative properties

References

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Kunz D and Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res* 2010;19(4):591–6.

Luthringer R, Muzet M, Zisapel N, *et al*. The effect of prolonged-release melatonin on sleep measures and psychomotor performance in elderly patients with insomnia. *Int Clin Psychopharmacol* 2009;24(5):239–49.

Memantine

Memantine was licensed for the treatment of Alzheimer's disease (AD) in the UK in 2002. It is the only agent licensed for the symptomatic management of dementia that is not a cholinesterase inhibitor. It may have a milder side effect profile than cholinesterase inhibitors.

Uses

Licensed uses

In the UK/USA

- *AD*: memantine is licensed for the symptomatic treatment of moderate-to-severe AD in individuals aged 18 and older.

In the UK, NICE recommends use in moderate disease only when patients are intolerant to, or have a contraindication to, AChEIs.

Off-label uses

- Dementia with Lewy bodies (DLB), mild to moderate Vascular Dementia (VaD), and combination therapy with donepezil in the management of AD.

Presentation

- *Trade names*: Alzhok®, Ebixa®, Marixino®, Memantine Accord®, Namenda®, Namenda XR®, Nemdatine®, and Valios®. Generics are not available.
- *Formulations*: memantine is available as an extended-release tablet, an oral solution, and a standard tablet. Extended-release tablet: 7 mg, 14 mg, 21 mg, and 28 mg. Oral solution: 2 mg/mL (USA) and 10 mg/mL (UK). Standard tablet: 5 mg, 10 mg, 15 mg, and 20 mg.

Mechanism of action

Memantine is a voltage-dependent, moderate-affinity, non-competitive *N*-methyl-D-aspartate receptor antagonist. This receptor controls synaptic plasticity and memory function. Memantine inhibits the prolonged influx of calcium ions from extra synaptic receptors that result in neuronal excitotoxicity. Memantine is also a non-competitive 5HT3 antagonist (effect unknown) and an antagonist at α-7 nicotinic AChRs (may contribute to worsening seen in early treatment with memantine).

Toxicity and side effects

- *Common—Cardiovascular*: hypertension. *Gastrointestinal*: constipation and deranged LFTs. *Immunological*: drug hypersensitivity. *Neurological*: disorders of balance, dizziness, and headache. *Psychiatric*: somnolence. *Respiratory*: dyspnoea.

- *Serious—Cardiovascular*: cardiac failure, thromboembolism including venous thrombosis. *Gastrointestinal*: pancreatitis has been reported. *Neurological*: seizures. *Psychiatric*: psychosis has been reported.

Contraindications

- *Absolute*: hypersensitivity to memantine or its excipients, CrCl <5 mL/min.
- *Relative*: caution in patients with cardiovascular disease and previous history of seizures. The dose should be adjusted in renal impairment. For the oral solution and standard tablet in moderate impairment (CrCl 30–49 mL/min), the usual maintenance dose should be 10 mg daily, increasing to 20 mg only if well tolerated after at least 7 days' treatment. In severe impairment (CrCl 5–29 mL/min), 10 mg/day is the maximum recommended dose. A maximum dose of 14 mg/day is recommended for the extended-release preparation in severe impairment. No dose adjustment is required in mild to moderate impairment. In mild or moderate hepatic impairment, all formulations of memantine are safe. No data are available on those with severe hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustment is required in this group.
- *Pregnancy*: intrauterine growth retardation has been reported in animal studies. There are no existing reports of the effect of memantine use in pregnant humans, and therefore it should only be used if benefits outweigh risks.
- *Lactation*: it is not known if memantine is present in breast milk; however, it is highly lipophilic, suggesting that it probably is. The manufacturer advises avoidance in breastfeeding mothers.

Efficacy

- *AD*: a 2006 Cochrane review conducted a meta-analysis of RCTs investigating the use of memantine in patients with AD, VaD, and mixed dementia. In patients with moderate-to-severe AD, memantine showed significant benefits on cognition (2.97 points on the 100-point severe impairment battery score, 95% CI 1.68–4.26; p <0.0001), activities of daily living (1.27 points on the 54-point Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) severity score, 95% CI 0.44–2.09; p = 0.003), behaviour (2.76 points on the 144-point Neuropsychiatric Inventory (NPI) score, 95% CI 0.88–4.63; p = 0.004), and clinical impression of change (0.28 points on the 7-point Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) score, 95% CI 0.15–0.41; p <0.0001) after 6 months of treatment. Therefore, it is recommended for the treatment of moderate-to-severe AD.
- In the *DOMINO-AD* trial (Donepezil and Memantine in Moderate-to-Severe Alzheimer's Disease), an RCT of 295 patients with moderate-to-severe AD which investigated whether combination therapy with donepezil and memantine would be beneficial, it was established that

dual therapy did not confer statistically significant additive benefits in cognitive or global outcomes, compared with donepezil alone.

- *Other forms of dementia*: in the same Cochrane review mentioned above, data pooled from two RCTs of 20 mg/day of memantine in patients with mild to moderate VaD showed a small beneficial effect on cognition (1.85 ADAS-Cog points, 95% CI 0.88–2.83; $p = 0.0002$), as well as significantly less disturbed behaviour and reduced agitation. However, there was no significant effect on global clinical outcomes. As such, some clinicians advocate the use of memantine off licence in patients with mild to moderate VaD. There is no strong evidence to advocate the use of memantine in PDD or DLB.

Dosing and monitoring

Dosing

For the oral solution and standard tablet, start treatment at 5 mg od. This can be increased by 5 mg in 1-week intervals up to a maximum dose of 20 mg daily. The usual maintenance dose is 20 mg daily. When using memantine for mild to moderate VaD (off licence), the immediate-release preparation is advised, with a similar dosing and titration strategy as for AD.

For the extended-release preparation, start treatment at 7 mg od, and increase by 7 mg in weekly intervals to a recommended maintenance dose of 28 mg od.

Monitoring

Activities of daily living, behaviour, bowel function, cognitive function, and mood should be monitored while on treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Memantine has a bioavailability of ~100%. Peak plasma concentrations are reached at 3–8 h for immediate-release preparations, and 9–12 h for extended-release preparations. This is not affected by ingestion of food; however peak plasma concentrations are achieved earlier after administration with food in extended-release preparations. 45% of memantine is plasma protein-bound. Memantine undergoes partial hepatic metabolism into an *N*-glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine, independent of the cytochrome P450 system. 48% of the total dose is excreted unchanged in the urine. The rest is eliminated as inactive metabolites predominantly by the renal tract. The terminal half-life is 60–80 h.

Interactions

See Table 24.38.

Table 24.38 Interactions of memantine

Medications which alter memantine plasma levels	Medications whose plasma levels are altered by memantine	Pharmacodynamic interactions
Levels increased: carbonic anhydrase inhibitors, cimetidine, nicotine, procainamide, ranitidine, quinidine, quinine, sodium carbonate, and trimethoprim	Levels decreased: hydrochlorothiazide Levels increased: warfarin	With trimethoprim: may cause myoclonus and delirium With levodopa, dopaminergic agonists, and anticholinergics: effects of these medications may be increased

References

Howard R, McShane R, Lindesay J, *et al*. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *NEJM* 2012;366(10):893–903.

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Tan C, Yu J, Wang H, Tan M, *et al*. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2014;41(2):615–31.

Methotrexate

Methotrexate was initially used as a chemotherapeutic agent in acute lymphoblastic leukaemia in the 1950s. A role in treating rheumatoid arthritis was established in the 1970s, and it is now also used in a wide range of autoimmune neurological diseases.

Uses

Licensed uses

In the UK

- *Neuro-oncology*: methotrexate is licensed for use in a range of neoplastic conditions, including acute leukaemia, non-Hodgkin's lymphoma, sarcoma, and solid tumours of the breast, lung, head, and neck, among other neoplasms, in individuals of all ages.

In the USA

- *Neuro-oncology*: methotrexate is licensed for use in acute lymphoblastic meningeal leukaemia, mycosis fungoides or cutaneous T-cell lymphoma, trophoblastic neoplasms, breast, lung, and head and neck cancer, non-Hodgkin's lymphoma, among other neoplasms, in individuals of all ages.

Off-label uses

- Bechet's.
- GCA.

- Inclusion body myositis (IBM) (trial of therapy).
- Myasthenia gravis (second-line, chronic).
- Neurolupus (first-line, chronic).
- Neuromyelitis optica (second line).
- Neurosarcoidosis.
- Polymyositis /Dermatomyositis (first-line, chronic).
- Primary CNS lymphoma.
- Sjögren's syndrome.
- Vasculitis (first-line, chronic).

Presentation

- *Trade name*: Maxtrex®, Metoject®, Rheumatrex®, and Trexall®. Generics are available.
- *Formulation*: methotrexate is available as an oral tablet, (Maxtrex®, Rheumatrex®, and Trexall®), a pre-filled syringe for injection (Metoject®), and a vial for injection. Oral tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg. Pre-filled syringe (50 mg/mL): 0.15 mL, 0.2 mL, 0.25 mL, 0.3 mL, 0.35 mL, 0.4 mL, 0.45 mL, 0.5 mL, 0.55 mL, and 0.6 mL. Vial (2.5 mg/mL): 2 mL. Vial (25 mg/mL): 2 mL, 4 mL, 8 mL, 10 mL, and 20 mL. Vial (100 mg/mL): 10 mL and 50 mL. Of note, only the 25 mg/mL solution for injection is suitable for intrathecal administration; other doses are hypertonic and should not be administered in this fashion.

Mechanism of action

Methotrexate competitively inhibits dihydrofolate reductase. This enzyme converts folate into tetrahydrofolic acid, a substrate required for DNA synthesis. This action inhibits DNA synthesis, repair, and therefore cellular replication, giving antineoplastic and immunosuppressant effects.

Toxicity and side effects

- *Common—Endocrine*: impotence and loss of libido. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, ulcerative stomatitis, and vomiting. *Haematological*: leucopenia. *Immunological*: vasculitis. *Ophthalmological*: conjunctivitis.
- *Serious—Cardiovascular*: pericarditis and thromboembolic events. *Dermatological*: hypersensitivity, Stevens–Johnson syndrome, toxic epidermal necrolysis. *Gastrointestinal*: gastrointestinal ulceration/bleeding, hepatic impairment (including acute necrosis, fibrosis), malabsorption, pancreatitis, and toxic megacolon. *Genitourinary*: acute kidney injury and defective oogenesis/spermatogenesis. *Gynaecological*: infertility, vaginal ulceration. *Haematological*: anaemia, bone marrow failure, hypogammaglobulinaemia, and thrombocytopenia. *Immunological*: increased risk of infections. *Neurological*: leukoencephalopathy and stroke. *Respiratory*: acute or chronic interstitial pneumonitis and pulmonary fibrosis or oedema.

Contraindications

- *Absolute*: hypersensitivity, active infections, immunodeficiency syndromes, significant renal or hepatic impairment, and significant anaemia, leucopenia, or thrombocytopenia.
- *Relative*: reduced doses of methotrexate should be used in patients with mild renal impairment. Caution and regular monitoring of LFTs are required in pre-existing hepatic impairment.

Use in special populations

- *Elderly*: the elderly experience an age-related decline in hepatic and renal function, and hence methotrexate should be used with extreme caution in the elderly, given the increased risk of toxicity.
- *Pregnancy*: it is teratogenic and contraindicated in pregnancy. Contraception should be used during, and for 6 months following the final dose.
- *Lactation*: breastfeeding is contraindicated.

Efficacy

- *Immunomodulation*: see relevant conditions.
- *Neuro-oncology*: within the context of primary central nervous system lymphoma (PCNSL), methotrexate has been demonstrated to result in complete remission, when used as part of a regimen including cytarabine, in 46%, and a partial response was identified in a further 23%.

With regard to the management of leptomeningeal metastases, methotrexate is the agent most commonly used for intrathecal chemotherapy. Early case series conducted in the 1980s have suggested that, in combination with whole brain radiotherapy, intrathecal methotrexate can yield a median addition survival of up to 5.7 months in patients who have demonstrated a response by 1 month.

Dosing and monitoring

Dosing

Oral doses of between 7.5 mg and 25 mg once per week are typically used for neuro-immune indications. The individual chapters contain further details on individual conditions.

In the context of neuro-oncology, methotrexate may be given PO, IV, or intrathecally. The dosage of methotrexate varies, depending on the BSA, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. The exact dose for intrathecal administration depends on age, as this better correlates with CSF volume than the BSA.

Monitoring

Prior to, and during, treatment monitoring includes FBC, LFTs, U&Es, urinalysis, and a clinical assessment of respiratory complications. CXR and lung function tests should also be performed before initiation. Some clinicians advocate the unlicensed use of 5 mg of oral folate on days when methotrexate is not used, to reduce side effects.

Pharmacokinetics and interactions

Pharmacokinetics

Doses of 0.1 mg/kg are completely absorbed in the gastrointestinal tract, but larger doses may not be. Food has been shown to delay absorption and reduce peak concentration. ~50% of the drug is bound to serum proteins. The majority of the drug is excreted unchanged in the urine, with a small amount excreted in the faeces. It can be retained for several weeks in the kidneys and for several months in the liver. The serum half-life is calculated to be 2–4 h following IM or oral administration of ff/kg, and this increases with increased doses.

Interactions

See Table 24.39.

Table 24.39 Interactions of methotrexate

Medications which alter methotrexate plasma levels	Medications whose plasma levels are altered by methotrexate	Pharmacodynamic interactions
Decreased levels: acetazolamide and neomycin Increased levels: acitretin, ciprofloxacin, NSAIDs, nitrous oxide, penicillins, phenytoin, probenecid, proton-pump inhibitors, and pyrimethamine	Decreased levels: digoxin Increased levels: theophylline	With ciclosporin, cisplatin, doxycycline, leflunomide, sulfamethoxazole, sulfonamides, tetracycline, and trimethoprim: there is an increased risk of toxicity With clozapine: there is also an increased risk of agranulocytosis

References

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Sause WT, Crowley J, Eyre HJ, *et al*. Whole brain irradiation and intrathecal methotrexate in the treatment of solid tumor leptomeningeal metastases – a Southwest Oncology Group Study. *J Neurooncol* 1988;6(2):107–12.

Methylphenidate

Methylphenidate has been used to treat narcolepsy since the 1950s. It is now more commonly used in the management of ADHD. It is a CNS stimulant, which is now second-line behind modafinil in the management of narcolepsy. Small studies have demonstrated its effectiveness in maintaining wakefulness; however, it is limited by its potential as a drug of abuse and for well-recognized cardiovascular, cerebrovascular, and psychiatric side effects.

Uses

Licensed uses

In the USA

- *Narcolepsy*: methylphenidate is licensed for the symptomatic treatment of narcolepsy in individuals >6 years of age.

In the UK

- Methylphenidate is licensed for the treatment of ADHD, but not for narcolepsy.

Off-label uses

- Other sleep disorders, including cancer-related fatigue.

Presentation

- *Trade names*: Methylin®, Ritalin®, and Ritalin SR® are the only formulations licensed in the USA for use in narcolepsy. Aptensio XR®, Concerta XL®, Equasym XL®, Matoride XL®, and Medikinet XL® are formulations used primarily in ADHD. Generics are available.
- *Formulations*: methylphenidate is available as a capsule, a modified (including extended/sustained)-release tablet, an oral suspension, and a standard tablet. Modified-release capsule/tablet: doses vary widely, depending on the formulation. Oral suspension: 60 mL, 120 mL, 150 mL, and 180 mL vials at a concentration of 25 mg/5 mL. Standard tablet: 5 mg, 10 mg, and 20 mg.

Mechanism of action

The mechanism of action of methylphenidate in narcolepsy and ADHD is not well understood. It is a CNS stimulant. Part of its action may be mediated by a combined action of both increasing releasing, and inhibiting uptake of dopamine and noradrenaline at presynaptic neurons. This acts to stimulate the brain's arousal pathways.

Toxicity and side effects

- *Common—Cardiovascular*: arrhythmia, hypertension, palpitations, and tachycardia. *Dermatological*: alopecia, pruritus, rash, and urticaria. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, dry mouth, nausea, vomiting, and weight loss (potentially resulting in growth failure in children). *Musculoskeletal*: arthralgia. *Neurological*: headache is very common. Dizziness, dyskinesia, fatigue, and psychomotor hyperactivity are common. *Ophthalmological*: blurred vision. *Psychiatric*: anorexia, insomnia, and mood disorders. *Respiratory*: cough and nasopharyngitis.
- *Serious—Cardiovascular*: rarely cardiac arrest and MI. *Dermatological*: anaphylaxis, angioneurotic oedema, and erythema multiforme. *Gastrointestinal*: hepatic coma has been reported. *Genitourinary:* priapism. *Neurological*: cerebral arteritis, movement disorders including tics, NMS, seizures, and strokes have been reported. *Psychiatric*: mania, psychosis, and suicidality are uncommon.

Contraindications

- *Absolute*: a diagnosis or history of psychopathic/borderline personality disorder, severe mood, or psychotic disorder. Pre-existing cardio- and cerebrovascular disease, including cardiomyopathies, cerebral aneurysm or vasculitis, CVA, haemodynamically significant congenital heart disease, heart failure, history of MI, life-threatening arrhythmias, peripheral vascular disease, and severe hypertension. In addition, hypersensitivity to methylphenidate or its excipients, hyperthyroidism, glaucoma, and phaeochromocytoma. Methylphenidate should also not be used concomitantly or within a month of use of irreversible MAOIs.
- *Relative*: epilepsy due to lowering of the seizure threshold. Patients with pre-existing history of drug abuse and with pre-existing cardio-/cerebrovascular disease or with vascular risk factors. Pre-existing psychiatric disorders, including mood, psychotic, and tic disorders. Methylphenidate has not been studied in hepatic and renal impairment; hence caution should be used, particularly in renal impairment, due to the extensive renal metabolism of the drug.

Use in special populations

- *Elderly*: methylphenidate has not been trialled in the elderly. The manufacturer advises against use in this population.
- *Pregnancy*: human cohort studies have suggested that first-trimester *in utero* exposure to methylphenidate does not have a significantly increased risk of major malformations. Studies have also not identified risk of miscarriage or adverse maternal or fetal outcomes. The advantages and disadvantages of ongoing use of methylphenidate in pregnancy should be discussed with the mother, and treatment decisions made on an individual basis.
- *Lactation*: methylphenidate is present in human breast milk although levels are low, and limited studies have suggested that it is undetectable in infants of breastfeeding mothers taking it. Large doses may impair mild production. If methylphenidate is used during lactation, then monitor for infant side effects and switch to an alternative feeding method if these are identified.

Efficacy

Evidence for the use of methylphenidate in narcolepsy is limited to the results of small studies conducted in the 1980/90 s. One small placebo-controlled study of 26 patients showed that treatment with methylphenidate significantly increased the patients' ability to stay awake vs. placebo. A further similar study by the same group demonstrated that methylphenidate resulted in a statistically significant improvement in sleep latency, as measured by the maintenance of wakefulness test and a subjective improvement in narcolepsy symptoms.

Dosing and monitoring

Dosing

- Immediate-release tablets/solution: start treatment at 5 mg bd at breakfast and lunch. This can be increased by 5–10 mg at intervals of 1

week up to a maximum of 60 mg, split over 2–3 doses, with an average dose being around 20–30 mg daily.
- Modified-release tablets: titrate initially with immediate-release tablets, then switch to modified-release tablets (over 8 h) at a later point.

Monitoring
- Prior to initiation of treatment, FBC, cardiovascular history, and vascular risk factor history should be taken. An FBC should be repeated regularly throughout treatment. BP, pulse rate, and, in children, height, weight, and appetite should be monitored 6-monthly. Patients should be regularly assessed for the emergence of psychiatric illness as well as for signs of abuse or dependence.

Pharmacokinetics and interactions

Pharmacokinetics

Methylphenidate is a racemic mixture of *d*- and *l*-enantiomers. The *d*-enantiomer is thought to be the active enantiomer. Bioavailability for the *d*-enantiomer is ~22%. Peak plasma concentrations occur ~1–2 h post. Bioavailability and peak plasma concentrations are enhanced by co-ingestion with food. Methylphenidate is 10–33% plasma-bound. The half-life is ~2 h. Methylphenidate is rapidly metabolized by CES1A1, a carboxylesterase; the metabolites are believed to have little pharmacological activity. Ultimately, >95% of the metabolized drug is excreted via the renal tract, <1% as unchanged methylphenidate.

Interactions

See Table 24.40.

Table 24.40 Interactions of methylphenidate

Medications whose plasma levels are altered by methylphenidate	Pharmacodynamic interactions
Levels increased: reports suggest methylphenidate may increase levels of coumarin anticoagulants, phenobarbital, phenytoin, primidone, SSRIs, and TCAs	With drugs that elevate BP, e.g. halogenated anaesthetics and irreversible MAOIs: may result in increase in BP/hypertensive crisis With alcohol and dopaminergic drugs, e.g. DOPA and TCAs: CNS effects may be exacerbated With clonidine: serious cardiovascular events, including sudden death, have been associated with this combination

References

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Mitler MM, Shafor R, Hajdukowik R, *et al*. Treatment of narcolepsy: objective studies on methylphenidate, pemoline and protriptyline. *Sleep* 1986;9(1 Pt 2):260–4.

Mexiletine

Mexiletine is a sodium channel blocker, initially used as an antiarrhythmic agent. Since 1983, it has been used off licence for the treatment of myotonia. It has recently received orphan designation in both the EU and USA, which has stimulated research in this area.

Uses

Licensed uses

In the USA

- Mexiletine has no licensed neurological uses.

In the UK

- Mexiletine is licensed for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

Off-label uses

- Treatment of myotonia in DM1 and non-dystrophic myotonias.

Presentation

- *Trade name*: Mexitil®, Namuscla®, Novo-Mexiletine®. Generics are available.
- *Formulation*: oral capsules of 150 mg, 167 mg, 200 mg, and 250 mg.

Mechanism of action

Mexiletine is a Vaughan–Williams class Ib antiarrhythmic that targets voltage-gated sodium channels. The non-dystrophic myotonias are characterized by delayed skeletal muscle relaxation. They are caused by mutations in either chloride channel (*CLCN1*) or sodium channel (*SCN4A*) genes. This results in an overactive ion channel and prolonged depolarization of the muscle fibre membrane. Mexiletine blocks the inward current in the sodium channel, thereby reducing the rate of rise of action potential and muscle fibre excitability.

Toxicity and side effects

- *Common—Cardiovascular*: bradycardia, chest pain, hypotension, prolongation of PR/QTc intervals/QRS duration, palpitations, syncope, tachycardia. *Dermatological:* acne, oedema, flushing, rash. *Gastrointestinal*: abdominal pain, dyspepsia, nausea, vomiting. *Musculoskeletal:* pain in extremities. *Neurological*: coordination difficulties, dizziness, headache, insomnia, paraesthesia, tremor. *Ophthalmological:* visual disturbance. *Respiratory:* dyspnoea.
- *Serious—Cardiovascular*: AV block, cardiogenic shock.

Contraindications

- *Absolute*: second- and third-degree AV block (if no pacemaker is present), cardiogenic shock, QTc prolongation.
- *Relative*: Dose adjustment is not required in renal impairment. In hepatic impairment, patients will often require lower doses and should be monitored closely. In these patients, the half-life is doubled, and the dose should be reduced by 25–30%.

Use in special populations

- *Elderly*: the elderly experience an age-related reduction in hepatic and renal function and are more prone to cardiovascular disease, and hence dose reduction is often required.
- *Pregnancy*: animal studies have not demonstrated fetal teratogenicity. There are no controlled studies in humans. The manufacturer advises caution in pregnancy and use only if benefit exceeds risks.
- *Lactation*: There is little data as to the effects of mexiletine in maternal milk on the infant. However, low levels are expected to be absorbed by the infant. In 2 cases the maximum dosage the infant received from breast milk was <2% of the maternally adjusted dose. Infants should be monitored for adverse effects and switched to an alternative feeding regimen if these are identified.

Efficacy

A multicentre, double-blind, placebo-controlled, cross-over study known as MYOMEX validated the efficacy and safety of mexiletine in patients with non-dystrophic myotonia. Patients receiving mexiletine had significantly lower stiffness scores over the 18-day treatment period, higher neuromuscular quality of life, and lower severity and disability global scores measured via the clinical myotonia scale. Another study on the long-term efficacy of mexiletine similarly found that the drug was both safe and effective in patients with non-dystrophic myotonia. Two small, randomized trials have demonstrated efficacy of mexiletine for myotonia in patients with DM1. In one, 150 mg tds mexiletine reduced grip relaxation time from 2.55s with placebo to 1.32s. Similar results were obtained for 200 mg tds mexiletine. Two randomized trials have shown that 200 mg tds mexiletine is an effective, safe, and well-tolerated treatment for myotonia-induced stiffness and pain in non-dystrophic myotonia. A short course (4–7 weeks) of mexiletine reduced handgrip myotonia by an average of 0.33s and improved patient-reported quality of life scores by 2.7 points, both of which were statistically significant.

Dosing and monitoring

Dosing

A typical dose for myotonia is 150–200 mg tds.

Monitoring

Patients should have a baseline ECG, and regular ECGs whilst on treatment to monitor the QRS duration and QTc interval.

Pharmacokinetics and interactions

Pharmacokinetics

Mexiletine has a bioavailability of 80–95%. The onset of action is 30–120 min, with peak plasma levels reached at 2–3 h. It is 50–60% protein-bound. The half-life is 10–14 h, longer in hepatic or cardiac failure. Metabolism is hepatic by CYP2D6 (and, to a lesser extent, CYP1A2), to largely inactive metabolites. Excretion is urinary (10–15% as unchanged drug).

Interactions

See Table 24.41.

Table 24.41 Interactions of mexiletine

Medications which alter mexiletine plasma levels	Medications whose plasma levels are altered by mexiletine
Levels decreased: amiodarone, cimetidine, ciprofloxacin, citalopram, cyproterone, efavirenz, fosphenytoin, furafylline, methoxsalen, phenytoin, quercetin, ribociclib, simeprevir, SSRIs, vemurafenib Levels increased: carbamazepine, cimetidine, darunavir, deferasirox, dexamethasone, modafinil, nafcillin, omeprazole, oritavancin, peginterferon α-2b, rifampin	Levels increased: bendamustine, clozapine, lidocaine, pirfenidone, pomalidomide, theophylline, tizanidine

References

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Heatwole C, Luebbe E, Rosero S, *et al*. Mexiletine in myotonic dystrophy type 1: a randomized, double-blind, placebo-controlled trial. *Neurol* 2021;96(2):e228–40.

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Vicart S, Franques J, Bouhour F, *et al*. Efficacy and safety of mexiletine in non-dystrophic myotonias: a randomised, double-blind, placebo-controlled, cross-over study. *Neuromuscul Disord* 2021;31(11):1124–35.

Midodrine

Midodrine was first used in the 1980s for the treatment of dysautonomia and orthostatic hypotension. It can be used in PD and other disorders associated with autonomic neuropathy for the management of orthostatic hypotension when conservative measures have failed.

Uses

Licensed uses

In the USA/UK

- *Orthostatic hypotension*: Midodrine is licensed for the treatment of symptomatic orthostatic hypotension, due to autonomic dysfunction, in patients not responding to standard clinical care in individuals aged 18 years and older.

Off-label uses

- None.

Presentation

- *Trade names*: Amatine®, Apo-Midodrine®, Bramox®, Gutron®, Midotense®, and ProAmatine®. Generics are available.
- *Formulations*: tablets: 2.5 mg, 5 mg, and 10 mg.

Mechanism of action

Midodrine is a prodrug with an active metabolite desglymidodrine which is a peripherally acting α1-adrenoceptor agonist. It increases the BP via vasoconstriction. Midodrine does not cross the blood–brain barrier and does not stimulate β-adrenergic receptors, and hence does not increase the heart rate.

Toxicity and side effects

- *Common—Cardiovascular*: supine hypertension (BP above or equal to 180/110mmHg) with daily doses above 30 mg (less commonly seen at lower doses). *Dermatological*: flushing, piloerection, pruritus (mainly of the scalp), and rash. *Gastrointestinal*: dyspepsia, nausea, stomatitis, and vomiting. *Neurological*: headache, paraesthesia. *Ophthalmological*: increased tear production. *Renal*: dysuria, urinary retention, and urgency.
- *Serious—Cardiovascular*: chest pain. *Neurological*: stroke.

Contraindications

- *Absolute*: hypersensitivity to midodrine or its excipients, severe organic heart disease, acute renal failure (creatinine clearance <30 mL/min), urinary retention, phaeochromocytoma, thyrotoxicosis, persistent and significant supine hypertension, serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms, serious prostate disorder, hyperthyroidism.
- *Relative*: patients with a history of urinary retention, diabetes, and glaucoma. Reduce the dose in renal impairment (2.5 mg ff tds, and gradually increase as tolerated). Caution should be taken in renal impairment, although no dose alteration is routinely recommended.

Use in special populations

- *Elderly*: no dose alteration is routinely required. The elderly experience an age-related decline in their renal function and are also more prone to hypertensive, cardiovascular, and cerebrovascular side effects, and hence cautious dose titration is recommended in this group.
- *Pregnancy*: animal studies showed adverse events. There is little data from human studies. Avoid in pregnancy and in women not using contraception, unless the possible clinical benefits clearly outweigh the potential hazards.
- *Lactation*: excretion in breast milk is not known. Use with caution in nursing mothers.

Efficacy

There is a lack of evidence for the use of midodrine specifically in PD-associated orthostatic hypotension. For this reason, it has been labelled as an investigational treatment in a recent MDS review. However, several trials have assessed its use in various causes of neurogenic hypotension where it was found to be efficacious, safe, and tolerable. A 6-week, randomized, double-blind multicentre study (n = 171) assessed midodrine (10 mg tds) against placebo for neurogenic hypotension. The primary endpoints were improvement in standing systolic BP, symptoms of light-headedness, and global symptom relief score. Midodrine resulted in significant improvements in standing systolic BP ($p < 0.001$), reported symptoms by the second week ($p = 0.001$), and global symptom relief score ($p = 0.03$). The main adverse effects were pilomotor reactions, urinary retention, and supine hypertension.

Dosing and monitoring

Dosing

Start treatment at 2.5 mg bd to tds, increasing gradually up to 10 mg tds. Supine hypertension is common (25%). The last dose should be taken 3–4 h before sleep to minimize nighttime supine hypertension. Some patients' orthostatic hypotension may worsen following commencement of midodrine.

It can be used alone or in combination with salt-retaining steroid therapy with or without salt supplementation, e.g. fludrocortisone acetate. However, patients on fludrocortisone should be carefully monitored for supine hypertension.

Monitoring

Regularly monitor the supine and sitting BP and renal function.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 93%. Absorption is not affected by food. Midodrine is a prodrug and is rapidly metabolized by deglycination, both hepatically and by other tissues, to desglymidodrine. The T_{max} of midodrine and desglymidodrine is 30 min and 1–2 h, respectively. The half-lives of midodrine and desglymidodrine are 25 min and 3–4 h, respectively. Elimination is predominantly by active renal secretion as desglymidodrine in the order of 385 mL/min.

Interactions

See Table 24.42.

Table 24.42 Interactions of midodrine

Medications whose plasma levels are altered by midodrine	Pharmacodynamic interactions
Levels decreased: With drugs metabolized by CYP2D6, e.g. tricyclic antidepressants, beta-blockers, SSRI, antiarrhythmics, promethazine, and MAO inhibitors type B	With β-blockers, calcium channel blockers, and cardiac glycosides: may enhance or precipitate their bradycardic effect, AV block, and arrythmia. With other vasopressors, e.g. ephedrine, phenylephrine, thyroid hormones: may increase their pressor effects. With MAO inhibitors or linezolid: avoid use with midodrine. With α-adrenergic blocking agents, e.g. doxazosin, prazosin, terazosin: these agents can antagonize the effects of midodrine

References

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Parsaik AK, Singh B, Altayar O, *et al*. Midodrine for orthostatic hypotension: a systematic review and meta-analysis of clinical trials. *J Gen Intern Med* 2013;28(11):1496–503.

Milrinone

Milrinone has been available since the late 1980s. It is licensed in both the USA and UK for the short treatment of severe cardiac failure. Due to its ability to induce vasospasm it is also used short term to treat cerebral vasospasm, in the context of neurovascular interventions and secondary to pathologies, including reversible cerebral vasospasm and subarachnoid haemorrhage.

Uses

Licensed uses

In the UK/USA

- Milrinone has no licensed neurological uses.

Off-label uses

- Treatment of cerebral vasospasm, including secondary to neurovascular procedures, reversible cerebral vasoconstriction syndrome, and subarachnoid haemorrhage.

Presentation

- *Trade names*: Primacor®. Generics are available.
- *Formulations*: Milrinone is available as a 10 mL ampoule for IA infusion. The 10 mL ampoule contains 10 mg of milrinone (1 mg/mL).

Mechanism of action

Milrinone, selectively inhibits cAMP phosphodiesterase type III isoenzyme in vascular smooth muscle cells, thereby increasing intracellular cAMP. This increases cAMP-dependent contractile protein phosphorylation and subsequent relaxation of vascular smooth muscle. This leads to vasodilatation.

Toxicity and side effects

- *Common— Cardiovascular:* hypotension, ventricular ectopy, non-sustained or sustained ventricular tachycardia and supraventricular arrhythmias (related to underlying risk factors rather than dose-/plasma level-related). *Neurological:* Headaches.
- *Serious – Immunological:* anaphylaxis *Respiratory:* bronchospasm (very rare). *Cardiologic:* torsades de pointes (very rare) and ventricular fibrillation (uncommon).

Contraindications

- *Absolute:* Hypersensitivity to milrinone or its excipients and hypovolemia.
- *Relative:* Shortly after myocardial infarction, hypokalaemia (needs to be corrected prior to administration to minimize the risk of arrhythmia), hypovolemia, prior aggressive diuretic therapy and supraventricular tachycardias (SVT) (Milrinone increases AV node conduction, hence stabilization with digoxin should be considered before using milrinone in patients with known SVT). Renal impairment significantly increases the terminal half-life of milrinone. Clinicians are advised to keep the loading dose unchanged but reduce the maintenance dose and titrate to hemodynamic response. No dose alterations are required in hepatic impairment.

Uses in special populations

- *Elderly*: No dose alteration is routinely required, however milrinone should be administered with caution as the elderly are more likely to haver renal impairment and are more prone to hypotensive side effects.
- *Pregnancy*: Animal studies have not demonstrated any cause for concern, however no human studies have been undertaken. Milrinone should only be used if the potential benefits outweigh the potential risks to the fetus.
- *Lactation*: It is unknown if milrinone is excreted in human milk. The potential benefits of using milrinone should be weighed against the potential risks to the infant. It would be reasonable to temporarily suspend breastfeeding during treatment.

Efficacy

Milrinone is often used for chemical angioplasty in instances of vasospasm during neurovascular interventions, however its use for this indication has not been systematically studied. Isolated case reports advocate the use of IA milrinone for the treatment of cerebral vasospasm, either in cases of subarachnoid haemorrhage or in reversible cerebral vasoconstriction syndrome (RCVS). Milrinone can also be helpful diagnostically to differentiate vasospasm from vascular stenosis secondary to other causes e.g. vasculitis.

Dosing and monitoring

Dosing

Load with 50μg/kg administered over 10 min. If required, then start a continuous infusion titrated between 0.375 μg/kg/min and 0.75 μg/kg/min (standard 0.5 μg/kg/min) according to hemodynamic and clinical response. The total dose should not exceed 1.13 mg/kg/day or an infusion rate of 45.0 μg/kg/hr.

Monitoring

Patients need close hemodynamic monitoring during administration.

Pharmacokinetics and interactions

Pharmacokinetics

Milrinone is 70–91% protein-bound at therapeutic concentrations. It has a mean terminal elimination half-life of 2.3 h. The elimination half-life was prolonged in patients with renal impairment, in proportion to the degree of impairment. Milrinone is excreted in the urine as milrinone (83%) and O-glucuronide metabolite (12%). 90% is recovered in the urine within the first 8 h post-IV administration.

Interactions

See Table 24.43.

Table 24.43 Interactions of milrinone

Pharmacodynamic interactions
With diuretics: Hypokalaemia and hypovolaemia can increase the risk of SVT.
With bumetanide or furosemide: This may lead to precipitation if co-administered in intravenous lines.

References

Bouchard M, Verreault S, Gariépy JL, *et al.* IA milrinone for reversible cerebral vasoconstriction syndrome. *Headache* 2009;49(1):142–5.

Kass-Hout T, Kass-Hout O, Sun CH, *et al.* A novel approach to diagnose reversible cerebral vasoconstriction syndrome: a case series. *J Stroke Cerebrovasc Dis* 2015;24(1):e31–7.

Laneuville M, Ding J, Shamy M, *et al.* Intra-arterial milrinone may differentiate fulminant RCVS from vasculitis. *Neurol* 2017;89(10):1093–4.

Schmidt U, Bittner E, Pivi S, *et al.* Hemodynamic management and outcome of patients treated for cerebral vasospasm with intraarterial nicardipine and/or milrinone. *Anesth Analg* 2010;110(3):895–902.

Mitoxantrone

Mitoxantrone was first used as a chemotherapeutic agent in the 1970s and continues to be used to treat a range of malignancies. It was shown to be effective in relapsing forms of MS in 1997 and is used as second-line treatment, given the risk of cardiotoxicity and leukaemia.

Uses

Licensed uses

In the USA

- *RRMS, SPMS, and progressive–relapsing MS (PRMS)*: mitoxantrone is licensed to reduce disability and frequency of clinical relapses in patients with worsening RRMS, SPMS, or PRMS.

It is not licensed in the UK for use in MS.

Presentation

- *Trade names*: Novantrone® and Onkotrone®. Generics are available.
- *Formulation*: vial of 2 mg/mL concentrate for IV infusion: 10 mL, 12.5 mL, and 15 mL.

Mechanism of action

Mitoxantrone is a topoisomerase II inhibitor that prevents DNA synthesis and repair. It intercalates into DNA via hydrogen bonding, leading to cross-links and strand breaks. It blocks the cell cycle in the G2-phase. It also inhibits B-cell, T-cell, and macrophage proliferation and function, and reduces the release of pro-inflammatory cytokine, e.g. IFN-γ.

Toxicity and side effects

- *Common—Dermatological*: alopecia, blue discoloration of nails/skin/whites of eyes, hair loss, mouth sores, and rash. *Gastrointestinal*: constipation, deranged LFTs, diarrhoea, dysgeusia, nausea, and vomiting. *Genitourinary*: blue-green discoloration of. *Gynaecological*: amenorrhoea. *Immunological*: fever. *Neurological:* confusion, headache, lethargy, and paraesthesia. *Psychiatric*: anxiety.
- *Serious—Cardiovascular*: arrhythmia , cardiomyopathy, congestive cardiac failure, myocardial infarction. *Dermatological*: extravasation causing erythema/necrosis. *Haematological*: acute myeloid leukaemia (0.3% of patients, 80% of whom were exposed to a dose >60 mg/m^2), anaemia, leucopenia, and thrombocytopenia. *Gastrointestinal:* gastrointestinal haemorrhage, hepatotoxicity, and pancreatitis. *Renal:* toxic nephropathy. *Respiratory:* dyspnoea. *Vascular:* haemorrhage.

Contraindications

- *Absolute*: hypersensitivity to mitoxantrone, other anthracyclines, and sulphites that may be produced during the synthesis of mitoxantrone. Patients with impaired left ventricular ejection fraction.
- *Relative*: bone marrow suppression. Hepatic impairment results in decreased mitoxantrone clearance. Thus, mitoxantrone is generally contraindicated in MS patients with hepatic impairment, although the drug can sometimes be administered to these patients if lower doses are given. The effect of mitoxantrone on patients with renal impairment has not been studied, and so mitoxantrone should be used with caution in these patients.

Use in special populations

- *Elderly*: mitoxantrone has not been studied in the elderly, and caution is advised.
- *Pregnancy*: this drug is contraindicated in pregnancy, due to potential teratogenicity. Contraception should be used during, and for 6 months following, treatment.
- *Lactation*: breastfeeding is contraindicated due to concerns about the effects of maternal antineoplastic drug therapy on infants.

Efficacy

The Mitoxantrone in MS (MIMS) study compared treatment with mitoxantrone at a dose of 12 mg/m^2 every 3 months with placebo. It showed a 60% reduction in the number of relapses per subject in the treatment group over 2 years. Two randomized, controlled studies found additional evidence supporting the efficacy of this drug, including reductions in new Gd-enhancing lesions on MRI, relapses, and progression of disability in mitoxantrone-treated patients.

Dosing and monitoring

Dosing

There are two commonly used regimens for mitoxantrone in MS: 12 mg/m^2 every 3 months for 2 years (MIMS protocol) or 20 mg administered with 1 g of IV methylprednisolone every 4 weeks for 6 months (French–British protocol).

Monitoring

Prior to treatment initiation, FBC, pregnancy test, cardiac examination, ECG, and echocardiography or multigated acquisition (MUGA) scan are performed. Regular FBC monitoring should be continued during treatment, and annual echocardiography should be continued indefinitely to measure for signs of cardiotoxicity. Quantitative reevaluation of left ventricular ejection fraction should be performed before each additional dose and every year after mitoxantrone treatment has ended in order to detect any signs of long-term cardiotoxicity. Patients should not receive a lifetime cumulative dose >140 mg/m^2 to minimize cardiotoxicity.

Pharmacokinetics and interactions

Pharmacokinetics

Mitoxantrone is given as an IV infusion. 25% of the active drug is metabolized to an inactive form and conjugated in the hepatobiliary system where it is excreted. 65% of unchanged drug is excreted in the urine. Mitoxantrone is excreted via the hepatobiliary and renal systems, with a variable terminal half-life of ~4 days.

Interactions

See Table 24.44.

Table 24.44 Interactions of mitoxantrone

Medications which alter mitoxantrone plasma levels	Pharmacodynamic interactions
Increased levels: ciclosporin, inhibitors of BCRP transporter (e.g. eltrombopag, geftinib)	With clozapine: there is an increased risk of agranulocytosis With cardiotoxic active substances, e.g. anthracyclines: there is an increased risk of cardiac toxicity. With antineoplastic agents and/or radiotherapy: there have been associations with the development of acute myeloid leukaemia and myelodysplastic syndrome. With live virus vaccines, e.g. yellow fever vaccination: there is an increased risk of infection and adverse reactions, e.g. vaccinia gangrenosa and generalized vaccidnia. Avoid administration of live virus vaccines during mitoxantrone therapy and during the 3 months following termination of therapy.

References

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Hartung HP, Gonsette R, König N, *et al*.; Mitoxantrone in Multiple Sclerosis Study Group (MIMS). Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002;360(9350):2018–25.

Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence report: the efficacy and safety of mitoxantrone (novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurol* 2010;74(18):1463–70.

Millefiorini E, Gasperini C, Pozzilli C, *et al*. Randomised placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997;244(3):153–9.

Mycophenolate mofetil

Mycophenolate mofetil was developed in the 1990s as an immunosuppressant for use in preventing rejection following transplantation. It has since been used in several autoimmune neurological diseases.

Uses

Licensed uses

In the UK/USA

There are no licensed neurological uses.

Off-label uses

Amongst others include:

- MG (second-line, chronic).
- NMO (second line).
- PM.
- DM.

Presentation

- *Trade names*: Arzip®, CellCept®, Ceptava®, Myfenax®, and Myfortic®. Generics are available.
- *Formulations*: mycophenolate is available as an oral capsule, (CellCept®), an oral suspension (CellCept®), an oral tablet (Arzip®, CellCept®, Ceptava®, Myfenax®, and Myfortic®), and a powder for IV infusion (CellCept®). Oral capsule: 250 mg. Oral suspension (1 g/5 mL): 175 mL. Oral tablet: 180 mg, 360 mg, and 500 mg. Powder for infusion: 500 mg vial.

Mechanism of action

Mycophenolate mofetil is a reversible inhibitor of inosine monophosphate dehydrogenase, an enzyme used in guanosine nucleotide synthesis. The drug inhibits B and T lymphocyte proliferation by preventing DNA synthesis.

Toxicity and side effects

- *Common—Cardiovascular*: hyper-/hypotension and tachycardia. *Dermatological*: acne, alopecia, and fungal skin infections. *Endocrine*: hypercholesterolaemia, hyperglycaemia, hyper-/hypokalaemia, hyperuricaemia, hypocalcaemia, hypomagnesaemia, and hypophosphataemia. *Gastrointestinal*: constipation, dyspepsia, flatulence, gastroenteritis, gingival hyperplasia, ileus, and stomatitis. *Genitourinary*: UTI. *Gynaecological*: candidiasis. *Haematological*: anaemia, leucocytosis/leucopenia, and thrombocytopenia. *Musculoskeletal*: arthralgia. *Neurological*: dizziness, headache, hypertonia, myasthenic syndrome, paraesthesiae, seizure, somnolence, and tremor. *Psychiatric*: agitation, anxiety, confusion, depression, and insomnia. *Respiratory*: cough, dyspnoea, pleural effusions, and respiratory tract infections.
- *Serious—Dermatological*: skin cancer. *Endocrine*: acidosis and hyper-/hypokalaemia. *Gastrointestinal*: colitis, gastrointestinal ulceration/bleeding, hepatic impairment, pancreatitis, and peritonitis. *Genitourinary*: acute kidney injury. *Haematological*: Leukopenia and pure red cell aplasia. *Immunological*: hypersensitivity and increased risk of infections and malignancies. *Neurological*: seizures. Progressive multifocal leucoencephalopathy has been reported. *Respiratory*: interstitial lung disease.

Contraindications

- *Absolute*: hypersensitivity to mycophenolate.
- *Relative*: dose reductions may be required in patients with severe renal impairment (most manufacturers recommend a maximum dose of 1 g BD if eGFR <25 mL/min/1.73^2). Dose adjustments are not required in those with hepatic impairment.

Use in special populations

- *Elderly*: the elderly experience an age-related decline in renal function, and hence renal function should be monitored. In general, similar dosing to the usual adult doses can be used in the elderly.
- *Pregnancy*: mycophenolate is contraindicated in pregnancy, and contraception should be used during, and for 6 weeks following, therapy. Two cohort studies following the use of mycophenolate in the first trimester identified foetal malformation rates of 11–25%.
- *Lactation*: Mycophenolate is present in breast milk at levels between 20–50% of the mother's weight-adjusted dosage. No adverse events have been reported in breastfeeding infants, but data is limited, and most manufacturers recommend an alternative method of feeding where possible.

Efficacy

See relevant conditions in Chapter 7, Other inflammatory disorders of the central nervous system.

Dosing and monitoring

Dosing

An oral dose of 0.25–1.5 g bd can be used. *Initial:* 250–500 mg twice daily; increase based on response and tolerability to a maintenance dose of 1 to 1.5 g twice daily (Meriggioli 2003; Sanders 2016). Onset of clinical response to mycophenolate may take up to 6 to 12 months, with a maximum effect not apparent until 1 to 2 years (Hehir 2010; Sanders 2016). See individual conditions in Chapter 7, Other inflammatory disorders of the central nervous system, for further information.

Monitoring

FBC needs to be assessed prior to initiation, and then weekly during the first month, twice monthly in the second and third months, and monthly thereafter to monitor for neutropenia. A pregnancy test is also required prior to initiation. Chickenpox can be fatal in the immunocompromised, and patients should be advised to seek medical help if they are not immune and become exposed.

Pharmacokinetics and interactions

Pharmacokinetics

Mycophenolate mofetil has an oral bioavailability of 94%. It undergoes complete pre-systemic metabolism to its active metabolite mycophenolic acid (MPA) by hydrolysis in the gastrointestinal tract and liver. Time to peak plasma concentration varies between formulations, but it is typically 1–3 h. Secondary peaks in serum concentrations occur after 6 h following enterohepatic recirculation. MPA is 97% bound to plasma albumin. MPA is further metabolized to an inactive form by glucuronyl transferase. Of an administered dose, 93% is excreted into the urine, with 6% in the faeces.

Interactions

See Table 24.45.

Table 24.45 Interactions of mycophenolate mofetil

Medications which alter mycophenolate plasma levels	Medications whose plasma levels are altered by mycophenolate	Pharmacodynamic interactions
Decreased levels: antacids, co-amoxiclav, colestyramine, iron supplements, metronidazole, norfloxacin, rifampicin, and sevelamer. Increased levels: aciclovir and ganciclovir	Increased levels: aciclovir and ganciclovir	Vaccinations may be less effective, and live vaccinations should be avoided

Natalizumab

Natalizumab is a monoclonal antibody used to reduce the rate of relapses in RRMS. Although highly effective, its long-term use in JC positive patients is associated with the risk of developing life-threatening PML.

Uses

Licensed uses

In the UK

- *Highly active RRMS*: natalizumab is indicated as a single DMT for those with '*rapidly evolving severe*' RRMS and those with '*high disease activity despite treatment*'.
- *Rapidly evolving severe RRMS* is defined as two or more disabling relapses in 1 year, with at least one gadolinium-enhancing lesion on brain MRI or a significant increase in T2 lesion load.
- *High disease activity despite treatment* is defined as either having at least one relapse in the previous year on IFN-β or glatiramer acetate with at least nine T2 hyperintense lesions on brain MRI or having one gadolinium-enhancing lesion. This includes patients with unchanged/increased relapse rates or ongoing severe relapses, as compared to the previous year.

In the USA

- *MS*: natalizumab is licensed for relapsing forms of MS.

Off-label uses:
None.

Presentation

- *Trade names*: Tysabri®. Generics are not available.
- *Formulation*: Pre-filled syringe 150 mg/mL: 1 mL. Vial of 20 mg/mL concentrate for IV infusion: 15 mL.

Mechanism of action

Natalizumab is a recombinant humanized anti-α_4-integrin antibody. It prevents the migration of leucocytes across the blood–brain barrier to sites of CNS inflammation. It binds to the $\alpha_4\beta_1$-integrin molecule present on the surface of lymphocytes. This inhibits binding of integrin to the vascular cell adhesion molecule 1 (VCAM-1) endothelial receptor that mediates the migration of leucocytes into the brain parenchyma.

Toxicity and side effects

- *Common—Dermatological*: urticaria. *Gastrointestinal*: nausea and vomiting. *Genitourinary*: UTI. *Immunological*: fever and rigors. *Musculoskeletal*: arthralgia. *Neurological*: dizziness, fatigue, and headache. *Respiratory*: nasopharyngitis.
- *Serious—Gastrointestinal*: hepatic impairment. *Immunological*: anaphylaxis, immune reconstitution inflammatory syndrome (IRIS) on drug withdrawal, and opportunistic infections. *Neurological*: PML (see Progressive multifocal leukoencephalopathy, p. 659).

Contraindications

- *Absolute*: hypersensitivity, PML, pre-existing immunosuppression, concurrent IFN-β or glatiramer acetate treatment, and active malignancy (excluding basal cell carcinoma).
- *Relative*: the effect of the drug on patients with hepatic and renal impairment has not been studied, but liver function can be exacerbated with this drug. Regular LFT monitoring in patients with hepatic impairment is advised, but initial dose adjustment is not necessary.

Use in special populations

- *Elderly*: natalizumab has not been studied in the elderly.
- *Pregnancy*: Data from >700 exposed pregnancies suggest natalizumab does not result in an increased risk of early pregnancy complications or fetal malformations. Natalizumab does not cross the placental barrier in the first trimester but is actively transported from the second trimester onwards. Ongoing exposure late in pregnancy is associated with a reversible anaemia and thrombocytopaenia. Hence Natalizumab can be continued in pregnancy if benefits outweigh risks, but the Association of British Neurologists recommends considering pausing it from 34 weeks of gestation to 2–3 months post-partum.
- *Lactation*: Natalizumab is present in breast milk in small amounts but is likely to be digested by the infant's gastrointestinal tract. In small studies natalizumab is undetectable in blood samples from exposed infants. Breastfeeding is likely to be safe and most experts would not advise avoidance in this scenario.

Efficacy

The *AFFIRM* trial demonstrated a 68% reduction in the ARR at 1 year, compared to placebo, and a 42% reduction in sustained disability accumulation over 2 years, compared to placebo. MRI measures of disease activity were very significantly reduced by natalizumab, which produced a 92% decrease in gadolinium-enhancing lesions (means 2.4 vs. 0.2; $p < 0.001$), 83% decrease in new or enlarging T2 lesions (means 11 vs. 1.9; $p < 0.001$), and 76% decrease in new T1 hypointense lesions (means 4.6 vs. 1.1; $p < 0.001$), compared with placebo, over 2 years. Brain atrophy was greater in year 1 but significantly less in year 2, compared with the placebo group.

The *SENTINEL* study compared treatment with a combination of natalizumab and SC IFN-β1a with IFN-β1a alone and found significant benefits of combination treatment in terms of ARR and disability accumulation, but this was associated with an unacceptable increase in side effects, including two cases of PML. The ongoing Tysabri Observational Program (TOP) has to date shown that 56% of treated patients remain free of clinical disease activity after 30 months and that the EDSS, a disability score commonly used in MS, remains stable after 4 years.

Dosing and monitoring

Dosing

This drug is administered as a 300 mg IV infusion lasting 1 h, every 4 weeks. Treatment is generally started once the patient has stopped taking IFN-β or glatiramer for 4–6 weeks. Other immunosuppressants may require different washout periods.

Monitoring

FBC, and liver and renal function are monitored every 4 weeks. Patients must be observed and monitored for signs of hypersensitivity during, and for 1 h following, the first infusion, and then during subsequent infusions. A course of corticosteroids on treatment withdrawal should be considered to minimize the severity of IRIS, which is very common and occurs within 3 months of cessation of natalizumab. Antibodies against natalizumab can develop following treatment. These antibodies predispose to hypersensitivity reactions and decrease efficacy. Assays are commercially available and are recommended in the event of poor response to treatment or prominent infusion reactions.

Progressive multifocal leukoencephalopathy

PML is an opportunistic CNS infection caused by JC virus (JCV). It carries a 20–25% mortality rate. Risk is increased if there has been prior immunosuppression use (not including immunomodulation with IFN-β or glatiramer), with longer duration of natalizumab treatment (especially >2 years), with higher JCV antibody index values and JCV seropositivity (which reflects prior exposure to JCV and is present in ~50% of the population).

Anti-JCV antibody assays are taken prior to therapy to assess PML risk and monitored every 6 months. A negative result is associated with a risk of one case of PML per 10 000 patients treated with natalizumab (for at least 18 months). Patients positive for anti-JCV antibody are at increased risk (see risk stratification in Table 24.46). Seroconversion from JCV-negative to positive status occurs at a rate of 1–2% per annum, so JCV status must be repeated regularly (current recommendation is every 6 months) throughout treatment to accurately estimate risk.

MRI is performed before treatment and is repeated annually in low-risk patients (JCV-negative or treatment duration <2 years) and 6-monthly in higher-risk patients. Patients are screened for symptoms of PML prior to each infusion. Symptoms of PML include subacute onset of behavioural change or neuropsychiatric symptoms, aphasia, hemiparesis, hemianopia, and seizures.

Table 24.46 PML risk stratification for anti-JCV antibody-positive patients (as of 2016)

Natalizumab exposure	Without prior immunosuppression	With prior immunosuppression
0–2 years	<1/1000	1/1000
2–4 years	2/1000	6/1000
4–6 years	4/1000	7/1000
6–8 years	2/1000	6/1000

Source data from www.tysabri.com.

If PML is suspected, treatment is withheld, and MRI brain plus gadolinium and CSF examination for JCV are performed. Early recognition, early termination of natalizumab, and younger patients, with less co-morbidities are probably associated with better outcomes.

Pharmacokinetics and interactions

Pharmacokinetics

Natalizumab rapidly distributes within the intravascular volume, and steady-state concentrations are reached at 36 weeks. Clearance is unaffected by age, gender, or renal or hepatic function; however, antibodies against natalizumab can increase clearance 3-fold. Natalizumab has a half-life of 16 days. Treatment effects persist for up to 12 weeks.

Interactions

None.

References

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Miller DH, Soon D, Fernando KT, *et al*.; AFFIRM Investigators. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurol* 2007;68(17):1390–401.

Polman CH, O'Connor PW, Havrdova E, *et al*.; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *NEJM* 2006;354(9):899–910.

Rudick RA, Stuart WH, Calabresi PA, *et al*.; SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *NEJM* 2006;354(9):911–23.

Nimodipine

Nimodipine is an orally administered calcium channel blocker that has an increased selectivity for cerebral arterioles. It is the only agent licensed to prevent cerebral vasospasm following aneurysmal subarachnoid haemorrhage (SAH).

Uses

Licensed uses

In the UK/USA

- SAH: nimodipine is licensed for the prevention and treatment of ischaemic neurological deficits following aneurysmal SAH in individuals aged 18 years and older.

Off-label uses

- RCVS.

Presentation

- *Trade names*: Nimotop® and Nymalize®. Generics are not available.
- *Formulations*: nimodipine is available as a solution for infusion and a tablet. Tablet: 30 mg. Solution for infusion: 50 mL vial at 0.02%.

Mechanism of action

Nimodipine is a dihydropyridine L-type calcium channel receptor antagonist. In contrast to other calcium channel blockers, nimodipine has a higher affinity for the cerebral circulation. It acts to enhance cerebral perfusion, particularly in poorly perfused areas, and hence reduces the ischaemic effects arising secondary to vasospasm in SAH.

Toxicity and side effects

- *Common—cardiovascular*: hypotension and variation in heart rate. *Dermatological*: rash and sweating. *Gastrointestinal*: nausea. *Neurological*: headache. *Ophthalmological*: visual disturbance.
- *Serious*: *Cardiovascular:* Bradycardia. *Immunological:* Angioedema.

Contraindications

- *Absolute*: hypersensitivity to nimodipine or its excipients and within 1 month of MI or an episode of unstable angina. Acute porphyria.
- *Relative*: traumatic SAH (there is no evidence of benefit in this subgroup). In hepatic cirrhosis, the elimination may be reduced; hence the BP needs to be carefully monitored, and the dose reduced, if necessary. No dose adjustment is required in renal impairment, but renal function should be monitored if using an infusion.

Use in special populations

- *Elderly*: no dose adjustment is routinely required, but an age-related decline in hepatic and renal function, co-prescription of interacting medications, and an increased risk of hypotensive side effects means nimodipine should be used with caution in this group.
- *Pregnancy*: teratogenic effects have been noted in animal studies. Only use if the benefits outweigh the risks.
- *Lactation*: nimodipine is present in mammalian milk but at levels not expected to result in adverse effects in infants.

Efficacy

One trial has investigated the use of nimodipine (60 mg every 4 h for 21 days) in patients with a confirmed diagnosis of SAH. The incidence of infarction was 22% vs. 33% with placebo, a statistically significant RRR of 33% (95% CI 13–50%). Those treated with nimodipine also had significantly improved neurological outcomes. The findings in this study were reinforced in a meta-analysis that assessed the safety and efficacy of prophylactic nimodipine in patients with SAH; the meta-analysis demonstrated a 48% reduction in cerebral infarcts and a 38% reduction in the onset of delayed neurological deficits. Oral and IA nimodipine have been used in RCVS and may reduce the number and intensity of headaches, although formal trials in this disorder are lacking.

Dosing and monitoring

Dosing

For use in SAH, nimodipine should be started within 96 h of SAH at a dose of 60 mg every 4 h and continued for 21 days.

Monitoring

BP and heart rate should be monitored initially, particularly in patients with hepatic impairment.

Pharmacokinetics and interactions

Pharmacokinetics

Bioavailability is 13%, due to extensive first-pass metabolism. T_{max} is ~30–60 min. Co-ingestion of food reduces bioavailability and T_{max}. Over 95% of nimodipine is bound to plasma proteins. It is extensively hepatically metabolized, predominantly by the CYP3A4 isoenzyme, to inactive or weakly active metabolites. The plasma half-life is 1.7 h. 50% of metabolites are excreted in urine and 30% in faeces.

Interactions

See Table 24.47.

Table 24.47 Interactions of nimodipine

Medications which alter nimodipine plasma levels	Pharmacodynamic interactions
Levels decreased: rifampicin. Levels increased: cimetidine and grapefruit juice	With hypotensive agents, e.g. ACE inhibitors: enhanced hypotensive effect

References

Liu G, Luo J, Zhang L, *et al*. Meta-analysis of the safety and efficacy of prophylactic use of nimodipine in patients with an aneurysmal subarachnoid haemorrhage. *CNS Neurol Disord Drug Targets* 2011;10(7):834–44.

Pickard J, Murray G, Illingworth M. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ* 1989;298(6674):636–42.

Omaveloxolone

Omaveloxolone is the first approved therapy for Friedreich's ataxia based on a phase II double-blind study. It was first approved by the FDA in 2023, and has not yet received approval in the UK.

Uses

Licensed uses

- *In the USA (Not licensed for use in the UK)*
- Omaveloxolone is licensed for the treatment of Friedreich's Ataxia (FA) in adults and adolescents aged 16 years and older.

Off-label uses

There are no **off-label uses**

Presentation

- *Trade names*: Skylarys™. Generics are not available.
- *Formulations*: Omaveloxolone is available as a 50 mg immediate-release capsule.

Mechanism of action

Frataxin deficiency in FA results in mitochondrial dysfunction and increased production of reactive oxygen species. Omaveloxolone has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which is a master regulator of cellular redox homeostasis. Omaveloxolone binds to KEAP1, which mediates proteosomal degradation of Nrf2. Newly synthesized Nrf2 then accumulates and forms a heterodimer with small musculoaponeurotic fibrosarcoma (sMAF) protein and induces transcription of antioxidant response element (ARE) sequences. The Nrf2-transcriptional network includes various cytoprotective proteins, including those involved in glutathione biosynthesis. Omaveloxolone also inhibits inflammation through Nrf2 repression of pro-inflammatory genes.

Toxicity and side effects

- *Common*—Cardiac*: elevated BNP and cholesterol levels, and palpitations. *Dermatological*: rash. *Gastrointestinal*: abdominal pain, diarrhoea, elevated liver enzymes (AST/ALT), nausea, vomiting. *Musculoskeletal*: back pain, muscle spasms. *Neurological*: Headache.

Contraindications

- *Absolute:* Omaveloxolone should be avoided in patients with severe hepatic impairment.
- *Relative:* The dose could be reduced in patients with moderate hepatic impairment. Reduce to 100 mg once daily with close monitoring and consider reduction to 50 mg once daily if adverse reactions noted. No dose adjustment is required in mild hepatic impairment or renal impairment.

Uses in special populations

- *Elderly*: No data is available in patients over 65.
- *Pregnancy*: No data is available from human studies. Animal studies identified evidence of developmental toxicity at levels of exposure similar to that in humans, hence women of childbearing age are advised to take contraception and avoid taking medication whilst on treatment.
- *Lactation*: No data is available in humans. Omaveloxolone was excreted in the milk of lactating rats following oral administration and developmental toxicity was noted. Nursing mothers are advised to avoid breastfeeding.

Efficacy

In a double-blind trial (phase II MOXIe trial), patients aged 16–40 years with a modified Friedreich Ataxia Rating Scale (mFARS) score between 20–80, were randomized at a ratio of 1:1 to receive omaveloxolone 150 mg once daily (n = 51) or placebo (n = 52). A significant (p = 0.034) difference in mFARS score (– 1.93 ± 0.90) was reported in the overall population [n = 103] (i.e. including patients with pes cavus) at week 48.

Dosing and monitoring

Dosing

150 mg once daily.

Monitoring

Measure ALT, AST, bilirubin, BNP, and lipids prior to starting omaveloxolone and every month for 3 months thereafter. Increases in ALT and AST were noted up to 5 times and 3 times the ULN in 16% and 31%, respectively. Maximal increases were noted at 12 weeks. Patients were generally asymptomatic. Elevations were normalized with dose reduction and discontinuation of omaveloxolone . If 5 times ULN or 3 timed ULN with liver dysfunction stop omaveloxolone and monitor LFTs. Consider restarting if LFTs normalize with closer monitoring and dose reduction (see hepatic impairment).

14% of patients had an increase in BNP >200 pg/mL compared to 4% in the placebo group. If heart failure develops this may require omaveloxolone discontinuation, notably heart failure is common in FA.

29% of patients treated with omaveloxolone were found to have cholesterol greater than the ULN at one or more time points. This returned to baseline 4 weeks after discontinuing treatment. Monitor lipids periodically and treat according to local guidelines.

Pharmacokinetics and interactions

Pharmacokinetics

Peak plasma concentration is reached within 7–14 h. Plasma concentration over 50 mg to 150 mg dose range increased in a dose-dependent and dose proportional manner, but maximum omaveloxolone plasma concentration (Cmax)

increased in a less than dose proportional manner over the dose range in healthy fasted subjects. A high-fat meal increased the Cmax and area under the concentration-time curve by 350% and 15% respectively compared to fasting. Omaveloxolone is 97% protein-bound. It is primarily metabolized by CYP3A4 with minor metabolism by CYP2C8 and CYP2J2 enxymes. >90% is excreted in the faeces. Omaveloxolone may reduce the efficacy of combined hormonal contraceptives.

Interactions

See Table 24.48.

Table 24.48 Interactions of omaveloxolone

Medications which alter omaveloxolone plasma levels	Medications whose plasma levels are altered by omaveloxolone
Levels decreased: CYP3A inducers. Levels increased: CYP3A inhibitors (e.g. itraconazole)	Levels decreased: CYP3A4 substrates (e.g. midazolam), CYP2C8 substrates (e.g. repaglinide), Combined oral contraceptives.

References

Lynch D, Chin M, Delatycki M, *et al.* Safety and efficacy of omaveloxolone in Friedrich Ataxia (MOXIe Study). *Ann Neurol* 2021;89(2):212–25.

Paroxetine

Evidence for Paroxetine's use in sleep disorders is solely derived from case study evidence and clinical experience. These studies have suggested differing effects on various sleep disorders, i.e. it is frequently cited as worsening features of RBD, while improving the symptoms of insomnia and night terrors. It is far more commonly used for psychiatric indications. It benefits from once-daily dosing; however, it is associated with risks of psychiatric adverse events, including suicidality and a withdrawal syndrome if treatment is ceased abruptly.

Uses

Licensed uses

In the UK/USA (Licensing is the same.)

- Paroxetine is licensed for a wide range of psychiatric disorders, including depression and anxiety. There is no licensed neurological use.

Off-label uses

- Insomnia and non-REM parasomnias, e.g. night terrors, sleep-walking.

Presentation

- *Trade names*: Brisdelle®, Paxil®, Paxil CR®, Pexeva®, and Seroxat®. Generics are available.
- *Formulations*: paroxetine is available as a capsule, an extended-release tablet, an oral suspension, and a standard tablet. Capsule: 7.5 mg. Extended-release tablet: 12.5 mg, 25 mg, and 37.5 mg. Oral suspension: 150 mL vial (10 mg/5 mL). Standard tablet: 10 mg, 20 mg, and 30 mg.

Mechanism of action

Paroxetine is a strong and selective inhibitor of serotonin uptake. The mechanism behind its effects on sleep disorders is not understood. SSRIs as a group can manipulate sleep architecture—they inhibit REM sleep and may result in sleep fragmentation. Sleep disorders are commonly associated with anxiety and depression; potentially, part of its mechanism may be through improvement in these underlying disorders. However, in case reports where paroxetine has been effective at treating night terrors—clinical impact is often after the first dose, rather than weeks to months later, as seen with depression.

Toxicity and side effects

- *Common—Dermatological*: sweating. *Gastrointestinal*: anorexia, changes in bowel habit and weight, dry mouth, nausea, and vomiting. *Genitourinary*: sexual dysfunction. *Metabolic*: increased cholesterol and hyponatraemia. *Neurological*: dizziness, headache, impaired concentration, insomnia, and tremor. *Ophthalmological*: blurred vision. *Psychiatric*: abnormal dreams, agitation, fatigue, and SSRI discontinuation syndrome (>30% of patients if treatment is stopped abruptly).
- *Serious—Dermatological*: angio-oedema, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been reported. *Gastrointestinal*: hepatitis associated with liver failure has been reported. *Neurological*: serotonin syndrome is very rare. *Ophthalmological*: acute glaucoma has been reported. *Psychiatric*: mania and suicidality have been reported.

Contraindications

- *Absolute*: hypersensitivity to the active drug or its excipients, patients in the manic phase of bipolar affective disorder and with concomitant use of linezolid (only to be continued in exceptional circumstances, with adequate monitoring for serotonin syndrome) and MAOIs (do not start an SSRI until 2 weeks after MAOI cessation).
- *Relative*: cardiac disease, diabetes mellitus, epilepsy (can lower seizure threshold), history of angle-closure glaucoma, bleeding disorders, and mania. In patients with severe hepatic or renal impairment, use reduced doses.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and may benefit from lower dosing regimens. In addition, bleeding and hyponatraemia are more common side effects in the elderly population.
- *Pregnancy*: human epidemiological studies have suggested an increased risk of cardiac septal defects when paroxetine is used in the first trimester, at a rate of ~2/100 vs. ~1/100 in the general population. When used in the third trimester, neonates should be monitored for serotonergic/withdrawal effects, including difficulty sleeping, hypoglycaemia, irritability, respiratory distress, and seizures. The risk of primary pulmonary hypertension in the newborn may also be increased 5-fold to an incidence of 1/200. Treatment should be avoided in pregnancy, where possible.

- *Lactation*: paroxetine is present in very low quantities in breast milk <4 ng/mL. No side effects have been observed in infants of nursing mothers taking paroxetine; hence use can be considered.

Efficacy

Robust trial evidence for the efficacy of paroxetine in non-REM parasomnias is lacking. Evidence is derived primarily from case studies and clinical experience. One case series of six patients published in 1997 demonstrated that, in patients treated with between 20 mg and 40 mg of paroxetine, half of patients had complete cessation of night terrors; the other three patients had reduction, but not complete cessation, of night terrors.

Dosing and monitoring

Dosing

Trial data suggest initiation should be similar to that used in dosing paroxetine for the management of depression and other psychiatric disorders. Start treatment at 10 mg od in the morning, and increase to a maximum of 40 mg daily, in 10 mg steps.

Monitoring

Patients should be monitored for psychiatric adverse events, specifically suicidality, in the first few months of treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Paroxetine undergoes substantial first-pass metabolism. This mechanism is saturable to some extent, giving non-linear kinetics to paroxetine absorption and rendering absolute bioavailability of different formulations difficult to assess. Food co-ingestion in single-dose studies reduced time to peak plasma concentration from 6.4 h to 4.9 h. Peak plasma concentration was ~30% higher with food. Steady state is reached at ~10 days. More than 90% is protein-bound.

Paroxetine is extensively hepatically metabolized, predominantly by conjugation with glucuronic acid and sulphate. These are pharmacologically inactive. Metabolism is partially undertaken by CYP2D6 which can become saturated and results in non-linear kinetics of paroxetine metabolism. The elimination half-life is ~21 h. Two-thirds of the drug is excreted by the kidneys, and the other third in the faeces; only 2% is excreted as the parent compound.

Interactions

See Table 24.49.

Table 24.49 Interactions of paroxetine

Medications which alter paroxetine plasma levels	Medications whose plasma levels are altered by paroxetine	Pharmacodynamic interactions
Levels decreased: CYP2D6 inducers, e.g. rifampicin. Levels increased: CYP2D6 inhibitors, e.g. cimetidine	Levels decreased: endoxifen, an active metabolite of tamoxifen synthesized through CYP2D6 metabolism. Levels increased: drugs metabolized by CYP2D6, e.g. anticoagulants, metoprolol, pimozide, procyclidine, risperidone, and TCAs	With serotonergic medications, e.g. linezolid, tramadol, etc.: increased risk of serotonergic syndrome With drugs known to increase bleeding risk, e.g. atypical antipsychotics, NSAIDs, TCAs: increased risk of bleeding. With MAOIs, including linezolid: increased risk of hypertensive crisis

References

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Wilson SJ, Nutt DJ, Alford C, *et al*. British Association for psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol* 2010;24(11):1577–600.

Penicillamine

Penicillamine was one of the first drugs to be used in the management of WD and acts as a copper chelator, lowering total body copper content. It is effective but carries a high rate of side effects, particularly in patients presenting with neurological symptoms of WD. In these patients penicillamine can cause paradoxical worsening in 5–22% of patients.

Uses

Licensed uses

In the UK/USA (Licensing is the same.)

- *Inborn errors of metabolism*: penicillamine is licensed for the treatment of WD in individuals of all ages.

Off-label uses

- None.

Presentation

- *Trade names*: Cuprimine®, Depen®, and Distamine®. Generics are available.
- *Formulations*: penicillamine is available as a capsule and a tablet. Tablet: 125 mg and 250 mg. Capsule: 250 mg.

Mechanism of action

WD is characterized by the accumulation of copper in the liver, brain, and other tissues. This occurs secondary to the impaired function of ATP7B, an enzyme required to bind copper to caeruloplasmin, allowing the release of copper into the bloodstream. Penicillamine is a copper-chelating agent, which binds copper atoms and is subsequently excreted by the urinary tract, thereby reducing total systemic levels of copper.

Toxicity and side effects

- *Common—Gastrointestinal*: anorexia, diarrhoea, nausea, and vomiting. *Immunological*: fever, lymph node enlargement, and rash in 30%.
- *Serious—Dermatological*: elastosis perforans, pseudoxanthoma elasticum, urticaria (all rare). *Haematological*: thrombocytopenia is common, and regular monitoring should be undertaken. Agranulocytosis, neutropenia, and aplastic anaemia are rare. *Immunological*: Goodpasture's syndrome, lupus-like reaction, MG, and nephrotic syndrome. *Neurological*: neuropathy is rare (see below), and prophylactic pyridoxine is often co-prescribed for patients with poor dietary intake, as penicillamine increases the requirement for this vitamin. In up to a quarter of cases where penicillamine therapy is initiated, deterioration of the neurological features of WD (rigidity, dystonia, dysarthria, and tremor) can occur over a period of 2 weeks to 12 months (commonly after 6 weeks). This may be due to the mobilization and redistribution of copper from the liver to the brain. *Renal*: proteinuria is common, and patients should have regular urinalysis. Haematuria is rare, but the drug must be withdrawn immediately if no alternative cause is identified . *Respiratory*: dyspnoea, pulmonary haemorrhage, and pulmonary fibrosis have been reported.

Contraindications

- *Absolute*: hypersensitivity to penicillamine, previous agranulocytosis, aplastic anaemia, or thrombocytopenia with penicillamine, lupus erythematosus, and moderate or severe renal impairment.
- *Relative*: concomitant use of nephrotoxic drugs and gold treatment. In addition, use with caution if previous adverse reactions to gold. In patients with mild renal impairment, use with caution, and regularly monitor renal function. No dose adjustment is required in hepatic impairment.

Use in special populations

- *Elderly*: elderly patients are more likely to have both age-related renal impairment and to experience adverse effects related to penicillamine treatment. Start treatment at 20 mg/kg daily in divided doses and use the smallest possible dose to control symptoms.

- *Pregnancy*: penicillamine has been shown to be teratogenic in rats. There are no human-controlled studies. There have been anecdotal reports of human congenital abnormalities, and hence it should be avoided in pregnancy, if possible, or used at the lowest effective dose.
- *Lactation*: Penicillamine was not detected in breastmilk in small studies. Reduced copper and zinc were noted in some mother's breastmilk. Based on these data penicillamine use during breastfeeding is likely safe but requires more robust studies and should only be used when deemed essential per manufacturing guidance.

Efficacy

Even though high-quality evidence regarding the efficacy of initial monotherapy in WD is lacking, clinical consensus and small studies suggest that penicillamine is the most effective treatment for patients with hepatic presentation of WD. Evidence suggests that the majority of patients in the preclinical stages of WD or with a neurological presentation show favourable clinical outcomes (remain asymptomatic or improve) when treated with penicillamine on a long-term basis; a systematic review showed favourable clinical outcomes in 80.6% of patients with neurological symptoms of WD. However, a significant proportion of patients (5.3–22%) may show neurological deterioration soon after initiation of therapy with penicillamine.

Dosing and monitoring

Dosing

Start treatment at 1500–2000 mg daily in divided doses. Drug efficacy is optimized when used in conjunction with a low-copper diet (below 1 mg of copper per day). A maximum daily dose of 2000 mg should not be continued for >1 year. Once there is a good response, the dose can be reduced to a maintenance dosing of 750–1000 mg daily. An overall negative copper balance (taking into account the analysis of 24 h urinary copper excretion and dietary copper intake) is considered a good response.

Monitoring

Weekly FBC and urinalysis for the first 2 months and monthly thereafter is recommended. If the platelet count falls below 120 000/mm^3 or WBCs below 2500/mm^3 or either parameter shows three consecutive falls within the normal references range, withdrawal of penicillamine should be considered. The drug can be restarted at a lower dose, once counts return to the normal range.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 40–70%. T_{max} is 1–3 h. Co-ingestion of food reduces bioavailability. It is 80% plasma protein-bound and is eliminated primarily by metabolism to a disulfide form before excretion in the urine. The half-life is 1–3 h.

Interactions

See Table 24.50.

Table 24.50 Interactions of penicillamine

Medications which alter penicillamine plasma levels	Medications whose plasma levels are altered by penicillamine	Pharmacodynamic interactions
Levels decreased: oral antacids or iron (administered within 2 h) and zinc	Levels decreased: digoxin (administered within 2 h) and zinc. Levels increased: levodopa	With gold or immunosuppressants: increased risk of blood dyscrasias With NSAIDs: increased risk of renal impairement

References

Chang H, Xu A, Chen Z, *et al*. Long-term effects of combination of D-penicillamine and zinc salts in the treatment of Wilson's disease in children. *Exp Ther Med* 2013;5(4):1129–32.

Czlonkowska A, Gajda J, Rodo M. Effects of long-term treatment in Wilson's disease with D-penicillamine and zinc sulphate. *J Neurol* 1996;243(3):269–73.

Kodama H, Anan Y, Izumi Y, *et al*. Copper and zinc concentrations in the breast milk of mothers undergoing treatment for Wilson's disease: a prospective study. *BMJ Paediatr Open* 2021;5:e000948.

Weiss KH, Thurik F, Gotthardt DN, *et al*. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. *Clin Gastroenterol Hepatol* 2013;11(8):1028–35.

Wiggelinkhuizen M, Tilanus ME, Bollen CW, *et al*. Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson disease. *Aliment Pharmacol Ther* 2009;29(9):947–58.

Perampanel

Perampanel was first marketed for use as an ASM in the UK in 2012. It was initially licensed as an adjunct in focal-onset epilepsy but has recently also demonstrated efficacy and been licensed for the management of primary generalized tonic–clonic seizures in drug-resistant patients.

Uses

Licensed uses

- In the UK *Epilepsy*: perampanel is licensed as an adjunct for the treatment of focal-onset seizures in individuals aged 4 or older and as an adjunct for primary generalized tonic–clonic seizures in individuals aged 7 years and older.

In the USA

- *Epilepsy*: perampanel is licensed as an adjunct for the treatment of focal-onset seizures in individuals aged 4 or older and as an adjunct for primary generalized tonic–clonic seizures in individuals aged 12 years and older.

Off-label uses

- None.

Presentation

- *Trade names*: Fycompa®. Generics are not available.
- *Formulations*: perampanel is available as an oral solution and film-coated tablet. Oral solution 0.5 mg/mL. Tablet: f, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg.

Mechanism of action

Perampanel selectively and non-competitively inhibits AMPA receptors. These are ion channels that open in response to glutamate and other mediators of rapid excitatory neurotransmission. *In vitro* and *in vivo* models show that AMPA receptor antagonists have potent antiepileptic activity. At high concentrations, perampanel also weakly inhibits NMDA receptors, which may also contribute to seizure suppression.

Toxicity and side effects

- *Common—Gastrointestinal*: changes in appetite and nausea. Weight may increase. *Musculoskeletal*: back pain. *Neurological*: dizziness and fatigue are the commonest side effects requiring discontinuation. Ataxia, confusion, dysarthria, and falls can also occur. *Ophthalmological*: blurred and double vision. *Psychiatric*: aggression and anxiety.
- *Serious*: *Dermatological*: Drug-related eosinophilia and systemic side effects, Stevens–Johnson syndrome. *Psychiatric*: Homicidal and suicidal thoughts (tend to be dose-related and usually occur in the first 6 weeks—can be exacerbated by alcohol.)

Contraindications

- *Absolute*: hypersensitivity to perampanel or any of its excipients.
- *Relative*: perampanel is associated with hostility and suicidality; it should be used with caution in patients with significant psychiatric disturbance. It is not recommended in moderate-to-severe renal impairment. No dose adjustment is currently recommended for mild renal impairment. Use in severe hepatic dysfunction is not recommended. In mild to moderate hepatic dysfunction, doses should be uptitrated no faster than fortnightly, and the maximum recommended dose is 6 mg/day in mild dysfunction and 4 mg/day in moderate dysfunction.

Use in special populations

- *Elderly*: the elderly appear to be particularly at risk of falls as a side effect, and hence this should be monitored for. Caution should be used in the context of polypharmacy to ensure potential drug interactions are avoided. Dose increases should only be performed at 2 week intervals at maximum.
- *Pregnancy*: limited data are available. Perampanel is not recommended in pregnant women. There have been no documented impairments to fertility in animal studies. There are no data about drug pharmacokinetics in pregnancy.
- *Lactation*: perampanel is excreted into mammalian milk. In 2 case studies of infants exposed to perampanel in breast milk, infant serum levels were at the lower levels of the effective range. No adverse events were reported. Breastfeeding can continue if benefits outweigh risks.

Efficacy

Results of a phase 3 clinical trial (a multicentre, double-blind, placebo-controlled trial in patients >12 years old) suggest that, as an adjunct in focal-onset epilepsy, 8 mg of perampanel resulted in a >50% reduction in seizure frequency in one-third of patients vs. 15% with placebo. A double-blind placebo-controlled study investigating the use of perampanel in the treatment of refractory primary generalized tonic–clonic seizures demonstrated a 50% responder rate of 58% vs. 35.8% in the placebo group ($p = 0.0059$). The dose trialled was 8 mg or the highest tolerated.

Dosing and monitoring

Dosing

Start treatment at 2 mg once at night . This can be increased by increments of 2 mg/day fortnightly, unless perampanel is to be co-administered with medications which act to shorten its half-life (see Table 24.51). If this is the case, then titration intervals of 1 week should be used. The normal maintenance dose is 4–8 mg/day, although a maximum of 12 mg/day can be used.

Monitoring

Renal and hepatic function should be assessed prior to starting treatment, particularly in the elderly.

Therapeutic drug monitoring

Plasma perampanel levels have wide interindividual variability and no absolute reference range has been defined with regards to seizure suppression or adverse effects.

Pharmacokinetics and interactions

Pharmacokinetics

Perampanel has an oral bioavailability of ~100%. The rate of absorption, but not the extent of absorption, is affected by food co-ingestion. T_{max} is between 30 min and 2 h, delayed by 1–3 h if food is co-ingested. Over 95% of perampanel is bound to plasma proteins. Steady state is reached in 2–3 weeks. Less than 2% of the medication is excreted unchanged in the urine. The rest is extensively hepatically metabolized by oxidation, primarily via CYP3A4 and to a lesser extent by CYP1A2 and CYP2B6, then by sequential glucuronidation. 70% of the metabolized product is excreted in the faeces, the rest via the renal system. The half-life is ~105 h. This is shortened to ~25 h by carbamazepine, and the clearance of perampanel is doubled by phenytoin and oxcarbazepine, and, to a lesser extent, by topiramate. Mild to moderate hepatic dysfunction lengthens the half-life to ~300 h.

Interactions

See Table 24.51.

Table 24.51 Interactions of perampanel

Medications which alter perampanel plasma levels	Medications whose plasma levels are altered by perampanel	Pharmacodynamic interactions
Levels decreased: carbamazepine, oxcarbazepine, phenytoin, rifampin, St John's wort, and topiramate Levels increased: ketoconazole	Levels decreased: carbamazepine, clobazam, lamotrigine, midazolam oxcarbazepine (metabolite not measured), and valproate	With alcohol: can lead to aggression, confusion, and low mood

References

French JA, Krauss GL, Steinhoff BJ, *et al*. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomised global phase III study 305. *Epilepsia* 2013;54(1):117–25.

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Rektor I, Krauss GL, Bar M, *et al*. Perampanel Study 207: long-term open-label evaluation in patients with epilepsy. *Acta Neurol Scand* 2012;126(4):263–9.

Steinhoff BJ, Hübers E, Kurth C, *et al*. Plasma concentration and clinical effects of perampanel—the Kork experience. *Seizure* 2019;67:18–22.

Phenobarbital

Phenobarbital was first marketed in the UK as an ASM in 1912. It is one of the oldest anti-seizure medications still in widespread use. In developing countries, the WHO has recommended its use first-line in most seizure types. In developed countries, it has been largely relegated to third-line behind benzodiazepines and phenytoin in the treatment of status epilepticus. It is a very effective broad-spectrum ASM. Its main advantage is its swift onset of action when given IV or IM. It also has a long half-life, allowing for once-daily dosing. Tolerance does not occur. Its disadvantages are its marked sedative and behavioural side effects, the need for frequent blood monitoring, and its significant pharmacokinetic interaction profile.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: phenobarbital is licensed for the treatment of all forms of epilepsy (UK: except absence seizures) in individuals of all ages.

Off-label uses

- None.

Presentation

- *Trade names*: Luminal®. Generics are available.
- *Formulations*: phenobarbital is available as an elixir, an oral solution, a solution for IV injection, and a tablet. Elixir: 15 mg/5 mL. Oral solution: 20 mg/5 mL. Solution for IM or IV injection: 30 mg/mL, 60 mg/mL, and 200 mg/mL in 1 mL ampoules. Tablet: 15 mg, 30 mg, 60 mg and 100 mg.

Mechanism of action

The primary mechanism of action of phenobarbital is probably through prolongation of the opening times of chloride ion channels in post-synaptic neuronal membranes. This acts to enhance GABA-mediated inhibition throughout the cerebrum. Some of its actions may also be mediated by decreasing intra-neuronal sodium concentrations, inhibiting calcium influx following neuronal depolarization, raising serotonin levels, and inhibiting NA uptake.

Toxicity and side effects

- *Common—Dermatological*: maculopapular rashes in 1–3%. *Endocrine*: osteopenia with long-term use. *Gastrointestinal*: cholestasis. *Genitourinary*: loss of libido and erectile dysfunction. *Musculoskeletal*: arthralgia, osteomalacia, rickets. *Neurological*: patients commonly experience a dose-dependent ataxia, cognitive impairment, drowsiness, dysarthria, lack of coordination, and nystagmus. This is reversible on withdrawal of the drug. The most frequent side effect in adults is sedation. The elderly may experience hyperactivity and irritability. *Psychiatric*: depression.
- *Serious—Dermatological*: rarely, hypersensitivity reactions, such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, can occur. *Gastrointestinal*: hepatitis can occur. *Haematological*: attacks of acute intermittent porphyria and agranulocytosis. *Immunological*: widespread multisystem hypersensitivity reactions can occur. *Psychiatric*: suicidal ideation has been reported. *Respiratory*: respiratory depression can occur.

Of note, uncommonly, anaemia and thrombocytopenia can occur, often related to folate deficiency. In addition, long-term use can result in diffuse musculoskeletal pain, Dupuytren's contracture, frozen shoulder, plantar fibromatosis, heel and knuckle pads, and Peyronie's syndrome.

Contraindications

- *Absolute*: acute intermittent porphyria, known hypersensitivity to barbiturates or its excipients, severe hepatic impairment, severe renal impairment, and severe respiratory depression.
- *Relative*: it is ineffective in the management of absence seizures. Caution in individuals at risk of osteopenia (they may benefit from prophylactic calcium and vitamin D supplements), in individuals with a mild to moderate degree of respiratory depression, and when treating children or the elderly. Lower doses of phenobarbital should be used in mild to moderate hepatic and renal impairment.

Use in special populations

- *Elderly*: the elderly are more susceptible to the sedative side effect of phenobarbital. In addition, they have an age-related deterioration in their renal and hepatic function, and hence benefit from lower dosing regimens.
- *Pregnancy*: there is clear evidence of risk to the fetus. Phenobarbital crosses the placenta. Vitamin K-deficient haemorrhagic disease of the newborn can be prevented by prophylactic treatment with vitamin K. Use in pregnancy involves weighing up potential benefits and side effects (see Anti-seizure medications in young women, p. 38).
- *Lactation*: phenobarbital is present in breast milk. Infant plasma levels can be 50–100% of the mother's. If used, infants should be monitored for potential side effects such as sedation, vomiting, not reaching milestones, and weight gain. Infants should also be monitored for withdrawal symptoms such as tremor if the medication is discontinued. Infant plasma levels can be assessed, and the infant switched to an alternative feeding regimen if side effects are identified.

Efficacy

There is very limited research data about the efficacy of phenobarbital in developed countries. In developing countries, the effectiveness of phenobarbital as a monotherapy in the treatment of multiple seizure types has been repeatedly demonstrated. Its advantage in these settings is its low cost. A recent study from an epilepsy clinic in north India showed that a year's treatment amounted to 11 American dollars, a quarter of the price of valproate and dramatically cheaper than the newer ASMs.

Dosing and monitoring

Dosing

The long half-life and slow accumulation of phenobarbital means that maintenance doses can be given on the first day.

- *For the treatment of all forms of epilepsy, except typical absence seizures*, age >18 years: start treatment at 1.5–4 mg/kg/day in once-daily doses at night. Maintenance dose is usually between 60 and 200 mg/day.
- *For the treatment of status epilepticus*: the loading dose should be 10–20 mg/kg at a rate of 25–100 mg/min. The solution for IV injection needs to be first diluted by 1 in 10 with water for injections.

Monitoring

FBC and LFTs can be considered prior to starting phenobarbital, but regular monitoring is usually not necessary. Vitamin D level, with dual-energy X-ray absorptiometry (DEXA) scans, is indicated for individuals at risk of osteoporosis.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 10–40 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Bioavailability is >90% via both PO and IM routes. Food co-ingestion can delay absorption but does not impact on bioavailability. T_{max} occurs in <4 h for both PO and IM injections. 45–60% is protein-bound within the plasma. Up to 80% of phenobarbital is metabolized by the cytochrome P450 system. There is a degree of autoinduction (CYP1A2, CYP2C9, CYP2C19, and CYP3A4); hence, if phenobarbital is used as monotherapy, the dose may need to be increased when steady state is reached at 2–3 weeks. The half-life is 53–118 h in adults. The two main metabolites are p-hydroxyphenobarbital and 9-*D*-glucopyranosylphenobarbital. These are both inactive and, following further metabolism, are renally excreted. ~25% of phenobarbital is eliminated unchanged in the urine.

Interactions

See Table 24.52.

Table 24.52 Interactions of phenobarbital

Medications which alter phenobarbital plasma levels	Medications whose plasma levels are altered by\ phenobarbital	Pharmacodynamic interactions
Levels decreased: antacids, folic acid Levels increased: chloramphenicol, dicoumarol, oxcarbazepine, phenytoin, sodium valproate, methylphenidate, and propoxyphene	Levels decreased: substrates of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzymes, including albendazole, doxycycline griseofulvin, indinavir, ketoconazole, lamotrigine, and anticoagulants: warfarin Levels increased: retigabine	With alcohol: can lead to aggression, confusion, and low mood

References

Krishnan A, Sahariah SU, Kapoor SK. Cost of epilepsy in patients attending a secondary-level hospital in India. *Epilepsia* 2004;45(3):289–91.

Meierkord H, Boon P, Engelsen B, *et al*.; European Federation of Neurological Societies. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol* 2010;17(3):348–55.

Tudur Smith C, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database Syst Rev* 2003;1:CD001904.

Pimavanserin

Pimavanserin is an atypical antipsychotic used in the treatment of PD psychosis. It has a novel mechanism of action. It is an inverse agonist and antagonist at 5-HT_2 receptors. The FDA first approved it in 2016. Its main benefit is its lack of significant extrapyramidal side effects, which sets it apart from other antipsychotics used for this indication.

Uses

Licensed uses

In the USA (Not licensed for use in the UK)

- Pimavanserin is licensed for the treatment of PD psychosis in individuals aged 18 years and older.

Off-label uses

- Dementia-related psychosis.

Presentation

- *Trade names*: Nuplazid™. Generics are not available.
- *Formulations*: Pimavanserin is available as a 17 mg oral tablet.

Mechanism of action

The exact mechanism of pimavanserin in the treatment of PD psychosis is unclear. However, it is likely to be mediated through its action as an inverse agonist and antagonist activity at 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors.

Toxicity and side effects

- *Common—Cardiovascular*: peripheral oedema. *Dermatological:* rash, urticaria. *Gastrointestinal*: constipation and nausea. *Neurological*: confusion, gait disturbance, somnolence. *Psychiatric*: agitation, aggression, hallucinations.
- *Serious—Cardiovascular:* prolonged QT interval. *Immunological:* angioedema.

Contraindications

- *Absolute*: Hypersensitivity to pimavanserin or its excipients. Avoid pimavanserin in patients with a prolonged QT syndrome, or in combination with other medications that may prolong the QT syndrome.
- *Relative*: Pimavanserin is not recommended in patients with hepatic impairment or in severe renal impairment CrCl<30 mL/min, as it has not been evaluated in these populations.

Use in special populations

- *Elderly*: No dose adjustment is required. No clinically meaningful differences in safety or efficacy were identified in individuals over the age of 75 years old, when compared to those aged 65–75 years old.
- *Pregnancy*: No data is available from human studies. In animal studies, administration of pimavanserin did not have any teratogenic effects. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: There is no data from animal or human studies. It is not known if pimavanserin is present in human milk. Nursing mothers should consider an alternative method of feeding if pimavanserin is administered whilst breastfeeding.

Efficacy

- A 6-week, randomized, double-blind, placebo-controlled study of 199 adults older than 40 years old with Parkinson's disease psychosis assessed the role of pimavanserin in the management of PD psychosis.

The primary outcome was improvement in the Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD). Overall there was a 5.79 point decrease in the SAPS-PD scores compared with a 2.73 point decrease seen with placebo (p = 0.001).

Dosing and monitoring

Dosing

Start treatment at the usual maintenance dose of 34 mg once daily. If patients are on strong CYP3A4 inhibitors e.g. clarithromycin and ketoconazole, reduce the maintenance dose to 17 mg once daily.

Monitoring

No routine monitoring is required.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of pimavanserin is approximately 100%. Food co-ingestion had no significant effect on bioavailability. Pimavanserin is predominantly metabolized by the hepatic CYP450 system. CYP3A4 metabolizes pimavanserin into its main active metabolite AC-279. The median Tmax for pimavanserin is 6 h. Pimavanserin is 97% protein-bound. The elimination half-lives of pimavanserin and its active metabolite AC-279 are 57 and 200 h, respectively.

Interactions

See Table 24.53.

Table 24.53 Interactions of pimavanserin

Medications which alter pimavanserin plasma levels	Pharmacodynamic interactions
Levels decreased: Strong or moderate CYP3A4 inducers Strong inducers: carbamazepine, phenytoin, and St. John's wort. Moderate inducers: efavirenz and modafinil. Levels increased: Strong CYP3A4 Inhibitors: e.g. clarithromycin and ketoconazole.	With drugs that prolong the QT interval:e.g.antipsychotics:ziprasidone, chlorpromazine, Class 1A antiarrhythmic, e.g. quinidine and procainamide, Class 3 antiarrhythmics, e.g. amiodarone and sotalol: Increased risk of arrhythmia.

References

Cummings J, Isaacson S, Mills R, *et al.* Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* 2014;383(9916):533–40.

Piracetam

Piracetam has been available in the UK since the 1970s. It is particularly useful in the treatment of myoclonic seizures, and may be the only effective medication in some patients with progressive myoclonic epilepsy syndromes.

Uses

Licensed uses

In the UK

- *Myoclonus:* Piracetam is licensed for the treatment of myoclonus of cortical origin, regardless of aetiology, in individuals aged 16 years and older.

In the USA

- Betahistine is not licensed for use in the USA.

Off-label uses

- Anti-ageing, anxiety, coagulation disorders, cognitive enhancer, depression, and the management of alcoholism.

Presentation

- *Trade names*: Myocalm® and Nootropil®. Generics are available.
- *Formulations*: piracetam is available as a film-coated tablet and an oral solution. Film-coated tablet: 800 mg and 1.2 g. *Oral solution:* 333.3 mg/mL.

Mechanism of action

Piracetam's mechanism of action is unclear. *In vitro* and *in vivo* studies have demonstrated improved cerebral blood flow, increased oxidative glycolysis, anticholinergic effects, reduced platelet aggregation and enhanced erythrocyte function (in patients with sickle cell anaemia studies have demonstrated deformability of the erythrocyte membrane is improved and Rouleau formation reduced).

Toxicity and side effects

- *Common—Gastrointestinal*: abdominal discomfort, nausea, and weight gain. *Neurological*: hyperkinesia.
- *Serious— Haematological:* haemorrhagic disorders have rarely been reported. *Psychiatric:* depression and hallucinations.

Contraindications

- *Absolute*: Hypersensitivity to piracetam, other pyrrolidone derivatives or any of its excipients. Due to its effects on coagulation and platelet action, avoid in cerebral haemorrhage. Avoid in Huntington's chorea and if eGFR <20 mL/min/1.73 m^2.
- *Relative*: Exercise caution in individuals at increased risk of bleeding, e.g. major surgery, gastric ulcer, etc. At eGFR 50–80 mL/min/1.73 m^2 2/3 of the normal dose should be used. At eGFR 30–50 mL/min/1.73 m^2 1/3 of the normal dose in two divided doses should be used. At eGFR 20–30 mL/min/1.73 m^2 1/6 of the normal dose as a single dose should be used. No dose adjustment is required if the patient has hepatic impairment.

Use in special populations

- *Elderly*: no dose adjustment is required. Use with caution, as the elderly are more prone to side effects and have an age-related impairment in renal function.
- *Pregnancy*: Some animal studies have demonstrated teratogenic effects; however, there are no controlled studies in humans. There is currently no data looking at whether piracetam pharmacokinetics changes during pregnancy. The manufacturer advises avoidance in pregnancy. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: The manufacturer advises avoidance in breastfeeding. If used, infants should be monitored for potential side effects such as fatigue and irritability. The infant should be switched to an alternative feeding regimen if these are identified.

Efficacy

There is limited clinical data on the efficacy of piracetam in the treatment of myoclonus. One multicentre, double-blind, cross-over trial of 20 patients with Unverricht–Lundborg disease demonstrated that piracetam led to marked improvement in motor impairment and functional disability compared to placebo ($p = 0.02$ and $p = 0.003$, respectively). The effects of piracetam were reported as rapid and long-lasting.

Dosing and monitoring

Dosing

Start treatment at 7.2 g daily in 2–3 divided doses. This can be increased by 4.8 g every 2–3 days up to a recommended maximum of 24 g daily. The normal maintenance dose is <20 g per day.

Monitoring

Coagulation tests as well as measurements of renal and hepatic function should be assessed at baseline and repeated every 6–12 months.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is approximately 100%. This is not affected by food co-ingestion. Tmax occurs at 0.5–1.5 h post-dose. Steady state is reached in 1–2 days. There is no protein binding. There is no hepatic metabolism. ~100% of piracetam is excreted unchanged by the renal system. The half-life in young men is ~5 h.

Interactions

Piracetam does not have any significant pharmacokinetic interactions. Given its effects on platelet function, care should be taken if used with other antiplatelet agents.

References

Genton P, Guerrini R, Remy C. Piracetam in the treatment of cortical myoclonus. *Pharmacopsychiatry* 1999;32(1):49–53.

Kälviänen R, Khyuppenen J, Koskenkorva P, *et al.* Clinical picture of EPM1-Unverricht-Lundborg disease. *Epilepsia* 2008;49(4):549–56.

Koshkiniemi M, Van Vleyman B, Hakamies L, *et al.* Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double-blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo. *JNNP* 1998;64(3):344–8.

Malykh A, Sadaie M. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. *Drugs* 2010;70(3):287–312.

Pizotifen

Pizotifen is an antihistamine that has both serotonin antagonist and antimuscarinic effects. It is used as a prophylactic agent in the management of migraine. It can take several weeks before an effect is seen, and use is limited by adverse effects, specifically anticholinergic effects, sedation, and weight gain.

Uses

Licensed uses

In the UK

- *Vascular headache*: pizotifen is licensed for use in the prevention of vascular headache, which includes migraine and cluster headache, in individuals aged 2 years and older.

Pizotifen is not licensed for use in the USA.

Off-label uses

- None.

Presentation

- *Trade names*: Pizotyline®, Sanomigran®. Generics are available.
- *Formulations*: it is available as a tablet and an elixir. Tablets: 0.5 mg and 1.5 mg. Elixir: 0.25 mg/5 mL.

Mechanism of action

The mechanism of action of pizotifen is unclear. It has antagonistic activity at the $5HT_2$ receptor, but this is unlikely to underlie its antimigraine effect, as other drugs with a similar action have no effect on migraine. It also has antihistaminergic (H1), antimuscarinic, anti-adrenergic effects ($\alpha1$ and $\alpha2$), and antidopaminergic effects, but specific antagonists at these receptors have also failed to show benefit in migraine.

Toxicity and side effects

- *Common—Endocrine*: increased appetite, weight gain. *Gastrointestinal*: dry mouth and nausea. *Neurological*: sedation.
- *Serious—Cardiac*: fluid retention. *Neurological*: seizures.

Contraindications

- *Absolute*: hypersensitivity to pizotifen. Patients with migraine who have a history of stroke, TIA, or cardiovascular disease.
- *Relative*: it should be used with caution in porphyria, and history of acute angle-closure glaucoma, epilepsy, and urinary retention. It can be used in hepatic and renal impairment, but patients should be monitored closely. Slower dose up-titration may be needed.

Use in special populations

- *Elderly*: elderly patients can receive the same dose as younger patients but may require closer monitoring, due to greater susceptibility to the antimuscarinic effects of pizotifen.
- *Pregnancy*: animal studies have not shown harmful effects from pizotifen, but data on its effects in human pregnancy are limited. Outcomes from small numbers of pizotifen-exposed pregnancies suggest no major cases of fetal malformation. Given the limited data pizotifen should only be used if the potential benefit outweighs the risk of harm.
- *Lactation*: pizotifen is found in breast milk. The concentrations are thought to be low, however given the lack of data, breastfeeding is not recommended.

Efficacy

A recent systematic review and meta-analysis included 8 RCTs and concluded that pizotifen was safe and potentially efficacious but required a modern clinical trial as available trials are decades old. From small studies it has been demonstrated to reduce the frequency of migraine and the amount of antimigraine treatment needed in the acute attack. In one randomized study, 70% of the patients in the pizotifen arm found a very good or good effect from using pizotifen, compared with only 11% in the placebo arm.

Dosing and monitoring

Dosing

Start treatment at 0.5 mg. This can be increased at 2- to 3-weekly intervals to a maximum daily dose of 4.5 mg which should be given in divided doses. No single dose should exceed 3 mg. The usual dose is 1.5 mg daily, taken as a single dose at night or in three divided doses.

Monitoring:

Monitor weight, and regularly review for sedative side effects.

Pharmacokinetics and interactions

Pharmacokinetics

Pizotifen has an oral bioavailability of 80%. Peak serum concentration is reached ~5 h after ingestion. More than 90% of the drug is protein-bound. Pizotifen undergoes extensive hepatic metabolism, mainly glucuronidation , and its main metabolite is *N*-glucuronide conjugate. It does not induce or inhibit the cytochrome P450 system. Co-ingestion of food does not affect bioavailability. 18% of the parent drug is excreted unchanged in the faeces; <1% of the drug is excreted unchanged renally. The remainder is excreted as metabolites, 62% in the urine and 24% in the faeces. The half-life is 26 h.

Interactions

See Table 24.54.

Table 24.54 Interactions of pizotifen

Pharmacodynamic interactions
With anticholinergics: enhanced cholinergic effect With sedatives (alcohol, antipsychotics): increased sedation

References

Fragoso YD, Lopes GC, Santos GM, *et al*. Pizotifen for the treatment of migraine. A systematic review and meta-analysis. *Headache Medicine* 2021;12(3):168–81.

Osterman P. A comparison between placebo, pizotifen and divascan in migraine prophylaxis. *Acta Neurol Scand* 1977;56(1):17–28.

Symon DN, Russell G. Double-blind placebo-controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995;72(1):48–50.

Pregabalin

Pregabalin was first marketed in the UK in 2004. It is a GABA analogue, designed to be more effective than gabapentin. It is licensed for use in epilepsy and neuropathic pain. It is well tolerated, has few pharmacokinetic interactions, and may be more effective than gabapentin for both indications.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: pregabalin is licensed for treatment as an adjunct of focal-onset seizures in individuals aged 18 years and older.
- *Neuropathic pain*: pregabalin is licensed for peripheral and central neuropathic pain in individuals aged 18 years and older (in the USA, licensing specifies use for post-herpetic neuralgia, painful diabetic peripheral neuropathy, fibromyalgia, and neuropathic pain associated with spinal cord injury).

Off-label uses

- Insomnia and PLMS.

Presentation

- *Trade names*: Lyrica®. Alzain ®. Axalid ®. Generics are available.
- *Formulations*: pregabalin is available as a capsule and an oral solution. Capsule: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg. Oral solution: 20 mg/mL.

Mechanism of action

Pregabalin is a GABA analogue which does not act directly on GABA receptors. Its main action is thought to be via binding to, and closing, voltage-gated N and P/Q presynaptic calcium channels, thereby reducing epileptiform activity and synaptic transmission along nociceptive pathways.

Toxicity and side effects

- *Common—Endocrine*: sexual dysfunction is common. *Gastrointestinal*: common side effects include appetite changes, dry mouth, constipation, flatulence, nausea, and weight gain. Less commonly, abdominal bloating, hypersalivation, reflux, and taste disturbance can occur. *Neurological*: dizziness/vertigo, headache, and fatigue are the most common neurological side effects. Less commonly, confusion, dysarthria, insomnia, memory impairment, myoclonus, paraesthesiae, parkinsonism, and tremor. *Ophthalmological*: blurred and double vision. *Psychiatric*: euphoria and irritability.
- *Serious—Cardiovascular*: arrhythmias, heart block, heart failure, and QT interval prolongation can rarely occur. *Dermatological*: there are reports of angio-oedema and Stevens–Johnson syndrome. *Gastrointestinal*: rarely, pancreatitis and hepatitis has been reported. *Haematological*: neutropenia. *Musculoskeletal*: rarely, rhabdomyolysis has been reported. *Ophthalmological*: reduced visual acuity and visual field defects. *Psychiatric*: depression and suicidal ideation have been reported. *Renal*: renal failure.

Contraindications

- *Absolute*: hypersensitivity to gabapentin, pregabalin, or any of its excipients.
- *Relative*: pregabalin may exacerbate myoclonus; hence it should be avoided in this context. Emergent myoclonic jerks in the treatment of focal seizures are a sign to stop treatment. Caution in individuals suffering from severe heart failure and in those with conditions where encephalopathy may be precipitated. Pregabalin is predominantly eliminated by the renal system. If eGFR is 30–60 mL/min/1.73 m^2, the maximum recommended dose is 300 mg daily. If eGFR is 15–30 mL/min/1.73 m^2, start treatment at 25 mg od, and increase to a maximum of 150 mg daily in 1–2 divided doses. If eGFR is <15 mL/min/1.73 m^2, start at 25 mg od up to a maximum of 75 mg od. Dosage adjustment is not necessary in hepatic dysfunction.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens. The elderly are also more at risk of side effects, including confusion, cognitive impairment, falls, and heart block/failure.
- *Pregnancy*: some animal studies have demonstrated teratogenic effects; however, there are no studies in humans. There are currently no data looking at whether the pharmacokinetics of pregabalin change during pregnancy. Use in pregnancy should be avoided where possible. There are case reports of neonatal withdrawal shortly after birth hence it is recommended that delivery is carried out in hospital rather than in the community.
- *Lactation*: Pregabalin is present in breast milk in low concentrations (~7–8% of the average maternal dosage) but there is not adequate data to say it is safe in breastfeeding. Until more data becomes available, an

alternate drug may be preferred If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

- *Epilepsy*: a Cochrane review, conducted in 2008, of four trials investigating pregabalin use as an adjunct in refractory focal-onset epilepsy concluded that pregabalin was significantly more effective than placebo. A further Cochrane review in 2012 investigating the use of pregabalin as monotherapy in the treatment of focal-onset epilepsy concluded that pregabalin was inferior, in terms of efficacy, to lamotrigine, although similar with regards tolerability.
- *Neuropathic pain*: a systematic review encompassing 19 studies with 7003 participants found pregabalin effective at doses of 300–600 mg in achieving at least 50% pain relief in patients with post-herpetic neuralgia (NNT 3.9, 95% CI 3.1–5.1), painful diabetic neuropathy (NNT 5.0, 95% CI 4.0–6.6), central neuropathic pain (NNT 5.6, 95% CI 3.5–14), and fibromyalgia (NNT 11, 95% CI 7.1–21). Two further systematic reviews have demonstrated that pregabalin was effective in providing pain relief post-spinal cord injury and with phantom limb pain.

Dosing and monitoring

Dosing

- *For all indications*: start treatment at 25 mg bd. Then increase at 1-week intervals by 50 mg in divided doses to a maintenance dose of 300 mg in 2–3 divided doses. It can be increased to a maximum of 600 mg in divided doses.

Monitoring

Hepatic and renal function testing should be monitored at baseline and yearly thereafter. Monitor the weight and BMI; consider assessing fasting cholesterol and glucose at baseline.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 2–8 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability is >90%. This is not dependent on the dose or food co-ingestion. T_{max} is faster, ~1 h in the fasted state, compared to with food co-ingestion when it is 2.5–3 h. Steady-state plasma levels are reached in 1–2 days. Pregabalin is not bound to plasma proteins and is not metabolized by the liver. More than 98% is eliminated unchanged by the renal system. Renal clearance is directly proportional to the eGFR. The half-life is ~6 h.

Interactions

See Table 24.55

Table 24.55 Interactions of pregabalin

Medications which alter pregabalin plasma levels	Medications whose plasma levels are altered by pregabalin	Pharmacodynamic interactions
Levels decreased: None	Levels decreased: None	With CNS depressants, e.g. alcohol and MAOIs: can increase sedative side effects

References

Guy S, Mehta S, Leff L, *et al*. Anticonvulsant medication use for the management of pain following spinal cord injury: systematic review and effectiveness analysis. *Spinal Cord* 2014;52(2):89–96.
Lozasdi D, Hemming K, Marson AG. Pregabalin add-on for drug-resistant partial epilepsy. *Cochrane Database Syst Rev* 2008;1:CD005612.
McCormick Z, Chang-Chien G, Marshall B, *et al*. Phantom limb pain: a systematic neuroanatomical-based review of pharmacological treatment. *Pain Med* 2014;15(2):292–305.
Wiffen PJ, Derry S, Moore RA, *et al*. Antiepileptic drugs for neuropathic pain and fibromyalgia – an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2013;11:CD010567.
Zhou Q, Zheng J, Yu L, *et al*. Pregabalin monotherapy for epilepsy. *Cochrane Database Syst Rev* 2012;10:CD009429.

Primidone

Primidone was first marketed in the UK as an ASM in 1952. It is rapidly broken down into its active metabolites: phenobarbital which accounts for the majority of its antiepileptic action, and phenyl-ethyl malonamide (PEMA). Principal disadvantages are sedative and behavioural side effects and its extensive pharmacokinetic interactions. It is occasionally useful when other drugs have failed in the treatment of focal-onset or generalized seizures and is second line for the treatment of essential tremor.

Uses

Licensed uses

In the UK

- *Epilepsy/myoclonus*: primidone is licensed for use as an adjunct or monotherapy in the treatment of akinetic attacks, focal-onset seizures, grand mal epilepsy, Jacksonian seizures, myoclonic jerks, and temporal lobe epilepsy in individuals of all ages.
- *ET*: primidone is licensed for the management of ET in individuals of all ages.

In the USA

- *Epilepsy*: primidone is licensed for use as an adjunct or monotherapy in the treatment of focal-onset, grand mal, and psychomotor seizures in individuals of all ages.

Off-label uses

- Holmes' tremor.

Presentation

- *Trade names*: Mysoline®. Generics are available.
- *Formulations*: primidone is available as a scored tablet in 50 mg and 250 mg doses.

Mechanism of action

Primidone is rapidly converted to phenobarbital which accounts for the majority of its antiepileptic action (see Phenobarbital, p. 674). Primidone has also been demonstrated to exert additional seizure protection, independent of phenobarbital. The mechanism for this additional ability and for the effect of primidone in ET has not yet been established.

Toxicity and side effects

In addition to the side effects associated with phenobarbital (see Phenobarbital, p. 674), there is often an initial toxic reaction which arises before phenobarbital or PEMA are detectable in the blood. This comprises ataxia, dizziness, drowsiness, nausea, and vomiting that may be initially debilitating, but a tolerance soon develops.

In addition to phenobarbital-related side effects, the following may occur.

- *Common—Dermatological*: rash. *Gastrointestinal*: nausea and vomiting. *Neurological*: apathy, ataxia, dizziness, and headache. *Ophthalmological*: visual disturbances.
- *Serious—Dermatological*: DRESS, Stevens–Johnson syndrome, toxic epidermal necrolysis. *Haematological*: pancytopenia (rare). *Immunological*: SLE. *Psychiatric*: psychosis has been reported.

Contraindications

- *Absolute*: hypersensitivity to primidone , phenobarbital, or any of its excipients. Porphyria.

See Phenobarbital, p. 674.

Use in special populations

- *Elderly/pregnancy/lactation*: see Phenobarbital, p. 674.
- *Lactation*: unmetabolized primidone can also accumulate in breastfed infants to levels similar to maternal plasma levels.

Efficacy

- *Epilepsy*: there are few studies on the clinical efficacy of primidone in the management of epilepsy. One recent RCT looked at the benefits of using primidone or valproate as an add-on in carbamazepine-unresponsive patients with focal-onset epilepsy. It demonstrated quite

clearly that 15% more patients could expect a reduction in their seizure frequency by at least 50% with valproate, compared to primidone.
- *ET*: a recent systematic review identified six small RCTs that assessed the use of primidone for ET. The average reduction in tremor was 59·9%. About half of patients with ET respond to primidone, but this response is moderate in most (50% reduction in tremor amplitude and improvement in rating scales), and this may not be sufficient for patients with advanced ET.

Dosing and monitoring

Dosing

- *Epilepsy*: start treatment at 125 mg once at night. Then increase by 125 mg every 3 days, until 500 mg/day is reached in two divided doses. Then the dose can be increased by 250 mg, in divided doses every 3 days. The normal maintenance dose is 0.75–1.5 g daily.
- *ET*: start treatment at 25 mg/day at bedtime. This can be titrated up every 3 to 7 days by 25 mg to a usual maintenance dose of 250 mg/day in 1–2 divided doses, as tolerated/required. Doses of up to 750 mg/day may be beneficial but with increased risks of adverse effects.

Monitoring

Consider vitamin D supplementation and DEXA scans in patients at risk of osteoporosis.

Therapeutic drug monitoring

For primidone levels, therapeutic blood concentration is known to be between 5 to 10 mg/mL.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of primidone is >90%. The effect of food co-ingestion on phenobarbital bioavailability is not known. T_{max} is 2–4 h in adults. Protein binding is 35%. Primidone reaches steady state in 2–4 days, phenobarbital in 15–30 days. Primidone is hepatically metabolized to phenobarbital and PEMA. Both are active metabolites, although the anticonvulsant potency of PEMA is markedly less than that of phenobarbital. Phenobarbital undergoes autoinduction, and hence a dosing increase may be required when plasma levels have reached steady state. The majority of primidone and its metabolites are renally excreted. During monotherapy, ~65% is excreted unchanged in the urine; with enzyme-inducing AEDs, this is reduced to ~40%. As with phenobarbital, the plasma half-life varies, depending on co-administration of enzyme-inducing medication and age. The

Table 24.56 Interactions of primidone

Medications which alter primidone plasma levels	Medications whose plasma levels are altered by primidone
Levels decreased: acetazolamide, carbamazepine, isoniazid, phenytoin (carbamazepine and phenytoin increase phenobarbital levels), St John's wort. Levels increased: clobazam, ethosuximide, and stiripentol	Levels decreased: Anti-seizure medications—carbamazepine, clonazepam, ethosuximide, lamotrigine, rufinamide, stiripentol, tiagabine, topiramate, valproate, and zonisamide. Antivirals: cobicistat, daclatasvir, dasabuvir, ledipasvir, nelfinavir, rilpivirine, ombitasvir+ paritaprevir, sofosbuvir, telaprevir. Antifungal—voriconazole, isavuconazole. Antineoplastic—tyrosine kinase inhibitors, ifosfamide. Anticoagulants—apixaban, dabigatran, rivaroxaban, ticagrelor. Cardiovascular agents—bosentan , nimodipine, dronedarone, macitentan, ranolazine. Hormonal agents: abiraterone, ulipristal. Also delamanid , lurasidone, mianserin, oxycodone, quetiapine , sertraline.

half-life in adults without co-administration of enzyme-inducing drugs is 7–22 h; with these drugs, it is 3–12 h.

Interactions
See Table 24.56

References

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Procarbazine

Procarbazine was first licensed for use in the late 1960s. It has multiple mechanisms of action, including alkylation. It rapidly diffuses across the blood–brain barrier and is commonly used as part of the PCV (procarbazine, lomustine, and vincristine) regimen for brain tumours. Its myelosuppressive effects are milder than lomustine, although it is limited by both pharmacokinetic and pharmacodynamic drug interactions.

Uses

Licensed uses

In the UK/USA (Licensing is the same.)

- *Hodgkin's lymphoma*: procarbazine is licensed for use in the management of Hodgkin's lymphoma (UK: in individuals aged 2 years and above; USA: in individuals of all ages), as part of a chemotherapy protocol.

Off-label uses

- CNS tumours, non-Hodgkin's lymphomas, and PCNSL.

Presentation

- *Trade names*: Matulane®. Generics are available.
- *Formulations*: procarbazine is available as a 50 mg capsule.

Mechanism of action

The precise mechanism of action is unclear. Procarbazine may act by inhibition of DNA, protein, and RNA synthesis via inhibiting transmethylation of methyl groups of methionine to tRNA. Procarbazine may also have a direct action on DNA synthesis via auto-oxidation and generation of hydrogen peroxide which disrupts the activity of DNA-bound proteins.

Toxicity and side effects

- *Common—Cardiovascular*: hypotension, syncope, and tachycardia. *Dermatological*: alopecia, dermatitis, herpes, hyperpigmentation, and urticaria. *Endocrine*: gynaecomastia. *Gastrointestinal*: anorexia, nausea, and vomiting are very common. Constipation, diarrhoea, hepatic dysfunction, and stomatitis can occur. *Haematological*: bone marrow suppression, resulting in anaemia, leucopenia, and thrombocytopenia, are very common but are usually reversible and rarely require cessation of treatment.
- *Serious—Endocrine*: irreversible azoospermia and ovarian failure have been reported. *Oncology*: secondary malignancies, such as acute myeloid leukaemia and lung cancer, have been reported with the use of procarbazine-containing chemotherapy regimens.

Contraindications

- *Absolute*: hypersensitivity to procarbazine or one of the formulations components and pre-existing severe bone marrow suppression. Avoid in severe hepatic and renal impairment.
- *Relative*: use with caution in cardiovascular and cerebrovascular disease, epilepsy, and phaeochromocytoma due to MAOI activity. Patients should also be advised to avoid tyramine-containing foods/drinks for the same reason. Caution in hepatic and renal impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and may benefit from lower dosing regimens.

- *Pregnancy*: human studies have demonstrated teratogenicity in patients taking procarbazine as part of a multi-agent regimen. Animal studies have confirmed that procarbazine alone is associated with fetal malformations. Women of childbearing age should be offered effective contraception and advised to avoid becoming pregnant.
- *Lactation*: procarbazine is present in breast milk is unknown. Mothers taking procarbazine should avoid breastfeeding.

Efficacy

Procarbazine is commonly used within the context of the PCV chemotherapy regimen. The regimen is most useful in chemotherapy-sensitive tumours, such as anaplastic oligodendroglioma, where studies have shown that average overall survival is increased from 30.6 to 42.3 months when PCV was given, in addition to radiotherapy, vs. radiotherapy alone. For further discussion, see Lomustine, p. 626.

Dosing and monitoring

Dosing

The dosage of procarbazine varies, depending on the BSA, level of bone marrow dysfunction, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines.

For the treatment of brain tumours, procarbazine is usually given in 4- to 6-weekly cycles as part of combination therapy, e.g. PCV. A typical regimen is 75 mg/m^2 on days 8–21 in four cycles, lasting 6 weeks each.

Monitoring

Prior to initiation of treatment, FBC, and renal and liver function should be assessed. After initiation of treatment weekly FBC is recommended for at least 6 weeks, and the treatment should be suspended temporarily if the WCC falls below 3000 $cells/mm^3$ or platelets fall below 80 000/mm^3. Liver and renal function should be assessed regularly throughout treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Procarbazine has good oral bioavailability and is rapidly absorbed, reaching peak plasma concentrations 12.5 min post-dose. There is good diffusion and distribution into the CSF. Procarbazine is rapidly broken down into its major metabolite azo-procarbazine, most likely by auto-hydrolysis. The half-life of procarbazine is 9.2 min. The specific metabolism of the azo-derivative is unclear; there are likely two main subsequent metabolites hydrazine and *N*-isopropylterephalamic acid, which are metabolized by a combination of hepatic and renal processes. Both are predominantly excreted in the urine.

Interactions

See Table 24.57.

Table 24.57 Interactions of procarbazine

Medications whose plasma levels are altered by procarbazine	Pharmacodynamic interactions
Levels decreased: phenytoin and cardiac glycosides	With alcohol: disulfiram-like reaction With cytotoxics and clozapine: may potentiate myelosuppressive effects. With amphetamine derivatives, SSRIs, SNRIs, noradrenaline–dopamine reuptake inhibitors (NDRIs), TCAs, anaesthetics containing adrenaline, and tyramine-containing foods: risk of hypertensive crisis secondary to MAOI effect. With enzyme-inducing anticonvulsants: predispose to procarbazine hypersensitivity reactions

References

Cairncross G, Berkey B, Shaw E, *et al*. Phase III Trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006;24(18):2707–14.

Van den Bent MJ, Brandes AA, Taphorn MJ, *et al*. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013;31(3):344–50.

Van den Bent MJ, Carpentier AF, Brandes AA, *et al*. Adjuvant procarbazine, lomustine and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomised EORTC phase III trial. *J Clin Oncol* 2006;24(18):2715–22.

Propranolol

Propranolol is a non-selective β-blocker. It has been used in the management of migraine and essential tremor (ET) since the 1960s. It is a relatively safe drug, with mainly cardiovascular and gastrointestinal side effects.

Uses

Licensed uses

In the UK/USA

- *Migraine*: propranolol is licensed for use in migraine prophylaxis in individuals aged 18 years and older.
- *ET*: propranolol is licensed for the management of ET in individuals aged 18 years and older.

Off-label uses

- None.

Presentation

- *Trade names*: Angilol®, Half-Inderal LA®, Inderal LA®, InnoPran XL®, Syprol®. Generics are available.
- *Formulations*: propranolol is available as a modified-release capsule, a modified-release tablet, an oral solution, and a standard tablet. Modified-release capsule: 80 mg and 160 mg. Modified-release tablet: 80 mg and 160 mg. Oral solution: 5 mg/ 5 mL, 10 mg/5 mL, 40 mg/ 5 mL, and 50 mg/5 mL. Standard tablet: 10 mg, 40 mg, 80 mg, and 160 mg.

Mechanism of action

Propranolol is a non-selective β-adrenoceptor antagonist, and its precise mechanism of action in ET and migraine prophylaxis is not fully understood. In ET, its effects are likely mediated, at least in part, by inhibition of peripheral β-adrenergic receptors, while, in migraine, it is postulated that β1-receptor blockade may modulate cerebral vascular tone. Propranolol may also reduce the frequency of migraine through interaction with serotonin pathways.

Toxicity and side effects

The commonest limiting side effect of propranolol is lethargy.

- *Common—Cardiovascular*: bradycardia, cold extremities, hypotension. *Dermatological*: exacerbation of psoriasis. *Endocrine*: dyslipidaemia, hyperglycaemia, hypoglycaemia, hyperkalaemia. *Gastrointestinal*: diarrhoea, nausea, vomiting. *Neurological*: dizziness, insomnia, lethargy. *Psychiatric*: depression.
- *Serious—Cardiovascular*: AV block, heart failure. *Haematological*: agranulocytosis. *Respiratory*: bronchospasm, pneumonitis, pulmonary fibrosis.

Contraindications

- *Absolute*: asthma, cardiogenic shock, COPD, hypersensitivity, hypotension, second- and third-degree heart block, severe sinus bradycardia, severe peripheral vascular disease, sick sinus syndrome, uncontrolled heart failure.
- *Relative*: depression, diabetes. In severe hepatic impairment, the bioavailability of propranolol is increased, and dose reduction is advised. A lower starting dose of 20 mg bd to tds is recommended, with close monitoring of the heart rate with dose increases. Mild/moderate hepatic impairment and renal impairment do not usually require reduced doses, but patients with severe renal impairment should have their heart rate closely monitored.

Use in special populations

- *Elderly*: a lower dose may be used to initiate therapy, as renal, hepatic, and cardiac diseases are commoner in this group and increase the risk of toxicity.

- *Pregnancy*: beta-blockers can restrict fetal growth. If used at the time of labour, they can cause neonatal bradycardia and hypoglycaemia. Propranolol should only be used in pregnancy if the benefit outweighs the risk.
- *Lactation*: although present in breast milk, there have been no reported adverse effects, so it is deemed safe to use.

Efficacy

- *ET*: a systematic review highlighted 13 double-blind, placebo-controlled studies. The average cohort size was 18 (9–33). Average study duration was 2.9 weeks (0–8 weeks). Tremor was shown to improve on average by 54%, as measured by accelerometry. There have been no long-term studies of propranolol use in ET, although tolerance is believed to develop in 15%.
- *Migraine*: a Cochrane review of propranolol in the prophylaxis of migraine looked at 58 studies with a total of 5072 participants. The review found that propranolol was better than placebo at reducing headache frequency but that patients in the propranolol group were more likely to experience adverse effects. Propranolol was found to be almost twice as effective as placebo (relative risk of response to treatment 1.94, 95% CI 1.61–2.35).

Dosing and monitoring

Dosing

Start treatment at 40 mg bd to tds (standard tablet) or 80 mg od (modified-release tablet). This can be increased by 40–80 mg every 2–3 weeks, as required/tolerated. The usual maintenance dose for ET is 120–320 mg/day and for migraine is 80–160 mg/day.

Monitoring

Patients should have their heart rate assessed regularly and ECG monitoring if they are at risk of bradycardia.

Pharmacokinetics and interactions

Pharmacokinetics

The bioavailability of propranolol is 25%, due to extensive first-pass metabolism. Peak plasma concentrations occur at 1–4 h post-dose. Co-ingestion with food increases the bioavailability but to a variable extent. The half-life is 3–6 h. About 90% of the drug is protein-bound. Propranolol comprises two enantiomers R (+) and S (−). R (+) tends to bind to albumin, while S (−) binds to α1 glycoprotein. Hepatic aromatic hydroxylation and N-dealkylation are believed to be the main routes of metabolism. The cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved. The main metabolite 4-hydroxypropranolol is active. The metabolites are mainly renally excreted, with only 1–4% appearing in the faeces.

Interactions See Table 24.58.

Table 24.58 Interactions of propranolol

Medications which alter propranolol plasma levels	Medications whose plasma levels are altered by propranolol	Pharmacodynamic interactions
Levels increased: chlorpromazine, cimetidine, dronaderone, fluvoxamine. Levels decreased: levothyroxine, phenobarbital, rifampicin	Levels increased: chlorpromazine, imipramine, rizatriptan	With diltiazem and verapamil: severe hypotension and AV node block With adrenaline, dobutamine, and NA: risk of severe hypertension and bradycardia With antihypertensives: increased risk of hypotension With amiodarone and other antiarrhythmics, including lidocaine: increased rick of myocardial depression

References

Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;2:CD003225.

Zesiewicz T, Elble R, Louis E, *et al*. Practice parameter: therapies for essential tremor report of the quality standards subcommittee of the American Academy of Neurology. *Neurol* 2005;64(12):2008–20.

Quinine

In the USA Quinine has a black box warning and is not recommended for use in nocturnal leg cramps due to the potential for severe and/or life-threatening side effects. Its use in the UK should be undertaken on a trial basis in well-informed patients after treatable causes and non-pharmacological measures are shown to be ineffective.

Uses

Licensed uses

In the UK/USA

- There are no licensed neurological uses.

Off-label uses

- Nocturnal leg cramps in adult patients.

Presentation

- *Trade name*: Qualaquin®. Generics are available.
- *Formulations*: quinine is available as a solution for IV injection and as an oral tablet. Solution for IV injection: 300 mg/mL. Tablet: 200 mg and 300 mg.

Mechanism of action

Muscle cramps are painful, involuntary muscle contractions. Their aetiology remains unknown; thus, any pharmacological therapy is empirical in nature. Hypotheses include hyperexcitable motor nerve terminals and spinal disinhibition, resulting in hyperactivity of motor neurons. Quinine is thought to increase the refractory period of the muscle, therefore reducing its response to repetitive stimulation.

Toxicity and side effects

- *Common—Cardiovascular*: dose-dependent QT prolongation, syncope. *Dermatological*: angio-oedema, flushed skin, rash. *Endocrine*: hypoglycaemia (particularly after IV administration). *Gastrointestinal*: abdominal pain, nausea, vomiting. *Neurological*: ataxia, headache, tinnitus, vertigo, weakness. *Ophthalmological*: blurred vision, photosensitivity. *Respiratory*: exacerbation of asthma, dyspnoea.
- *Serious—Cardiovascular*: cardiac arrest, ventricular arrhythmia. *Haematological*: agranulocytosis, aplastic anaemia, disseminated intravascular coagulation (DIC), HUS, TTP. *Neurological*: blindness. *Renal*: acute kidney injury.

Contraindications

- *Absolute*: hypersensitivity to quinine, mefloquine, or quinidine (cross-sensitivity reported); MG (as quinine has neuromuscular-blocking properties); optic neuritis (quinine may exacerbate this); glucose-6-phosphate dehydrogenase (G6PD) deficiency (may cause haemolysis); tinnitus; haemoglobinuria.
- *Relative*: dose reduction and frequency advised in chronic renal failure. Dose adjustment is not required in hepatic impairment.

Use in special populations

- *Elderly*: the half-life is doubled in the elderly, due, in part, to an age-related decline in renal function. The dose should be reduced to avoid accumulation and toxicity.
- *Pregnancy*: nearly half of pregnant women may suffer from leg cramps. Quinine is contraindicated due to its teratogenicity in the first trimester, and non-drug measures are preferred (stretching and massage of the affected muscle).
- *Lactation*: quinine is present in breastmilk at low levels. and the infant is unlikely to develop adverse effects, but the dose could still be sufficient to cause haemolysis if the infant has G6PD. The advice is to only use if benefits outweigh risks.

Efficacy

A meta-analysis of 23 controlled trials concluded that on average quinine reduces episodes of cramp (by 28%), intensity (by 10%), and days (by 20%), compared to placebo. However, a significant number (+3% risk difference, 95% CI 0–6%) of people suffered from minor adverse effects with quinine, compared with placebo. In 2010, the FDA issued cautions against the use of quinine for this indication, due to its extensive side effect profile and uncertainty over its efficacy. The MHRA echoed this statement in the UK, although quinine use may still be considered if leg cramps are severe or cause regular sleep disruption. There is no evidence to support the use of quinine or any other medication to control cramps in amyotrophic lateral sclerosis (ALS).

Dosing and monitoring

Dosing

Doses of 200–300 mg nightly for 4–6 weeks and continue for 3 months if symptomatic relief. Doses up to 500 mg have been used.

Monitoring

Medication review is recommended 3 months after initiation to assess efficacy of treatment. During the treatment course, FBC, LFTs, blood glucose, and ECG should be regularly monitored. Ophthalmological review should be considered if visual symptoms occur.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 76–88%, with no effect of food co-ingestion. T_{max} occurs at 2–4 h. Between 69% and 92% of the drug is protein-bound. It undergoes hepatic metabolism via CYP450 enzymes to several metabolites, with one major metabolite (3-hydroxyquinine) being pharmacologically active, but less so than the parent drug. The metabolites are predominantly excreted by the renal tract; 20% of the ingested drug is excreted unchanged in the urine.

Interactions

See Table 24.59.

Table 24.59 Interactions of quinine

Medications which alter quinine plasma levels	Medications whose plasma levels are altered by quinine	Pharmacodynamic interactions
Levels decreased: rifampicin. Levels increased: atazanavir, cimetidine, darunavir, fosamprenavir, indinavir, ritonavir, tipranavir, warfarin	Levels increased: amantadine, digoxin, flecainide, suxamethonium	With amiodarone, halofantrine, haloperidol, droperidol, mefloquine, moxifloxacin, pimozide, saquinavir, agents which prolong the QT interval: increased risk of ventricular arrhythmias

References

Connolly PS, Shirley EA, Wasson JH, *et al*. Treatment of nocturnal leg cramps. A crossover trial of quinine vs vitamin E. *Arch Int Med* 1992;152(9):1877–80.
El-Tawil S, Al Musa T, Valli H, *et al*. Quinine for muscle cramps. *Cochrane Database Syst Rev* 2010;12:CD005044.
Quinine: not to be used routinely for nocturnal leg cramps. *Drug Safety Update* 2010;3:3.

Riluzole

Riluzole was originally developed in the 1950s as a centrally acting muscle relaxant and was later employed for its anticonvulsant, sedative, and neuroprotective features. Riluzole was approved for use in MND in the 1990s.

Uses

Licensed uses

In the UK/USA

- MND: riluzole is licensed to extend life in patients with ALS in individuals aged 18 years and older.

Off-label uses

- Other phenotypic variants of MND, HD, and PD.

Presentation

- *Trade names*: Rilutek® and Teglutik® (oral suspension) Generics are available.
- *Formulations*: riluzole is available as an oral suspension: 5 mg/mL; 250 mL and 300 mL bottles. Tablet: 50 mg.

Mechanism of action

The mechanism of action of riluzole is not fully understood. Among its complex effects are inhibition of the presynaptic release of glutamate, as well as sodium, calcium, and potassium currents.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension, peripheral oedema, tachycardia. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, vomiting. *Neurological*: dizziness, headache, somnolence, paraesthesiae, vertigo, weakness.
- *Serious—Gastrointestinal*: hepatitis, pancreatitis. *Respiratory*: interstitial lung disease.

Contraindications

- *Absolute*: hypersensitivity to riluzole, hepatic disease, or baseline ALT >3x ULN.
- *Relative*: abnormal LFTs. No dose adjustments required in renal impairment.

Use in special populations

- *Elderly*: the elderly experience an age-related deterioration in hepatic and renal function, and hence caution is required.
- *Pregnancy*: riluzole is contraindicated, due to embryo toxicity in animal models.
- *Lactation*: Limited evidence highlights low levels in breastmilk. Adverse effects would not be expected.

Efficacy

In patients with ALS riluzole improves the probability of surviving 1 year by 9%, and median survival is increased by 3 months (17.7 months vs. 14.9 months with placebo). It has very little, if any, effect on secondary outcomes measures, e.g. muscle strength. Studies looking at use in late-stage disease (average vital capacity <60%) have not shown a significant improvement in survival time or muscle strength.

Dosing and monitoring

Dosing

Commence and continue at 50 mg bd, an hour before, or 2 h after, food.

Monitoring

Riluzole should be prescribed with care in those with known abnormal liver function. Regular monitoring of hepatic function is recommended (monthly for 3 months, then 3-monthly for a further 9 months, annually thereafter). The manufacturer advises discontinuation of riluzole if ALT levels are >5 times the ULN or if jaundice develops. Clinicians should have a low threshold for chest radiography if dry cough or dyspnoea develops, due to the risk of interstitial lung disease.

Pharmacokinetics and interactions

Pharmacokinetics

Riluzole has a bioavailability of 60%, which is affected by food intake. Fatty meals reduce peak blood levels by 45%. It is 96% bound to plasma proteins and has an elimination half-life of 12 h. With multiple-dose administration, a steady state is reached in <5 days. It undergoes hepatic metabolism by cytochrome P4501A2; therefore, concurrent usage of other inhibitors of CYP1A2, such as caffeine and cigarette smoking, should be avoided. Excretion is predominantly via the urine (85% as metabolites, 2% as unchanged drug) and faeces (5%).

Interactions—see Table 24.60.

Table 24.60 Interactions of riluzole

Medications which alter riluzole plasma levels
Levels decreased: cigarettes, charcoal-broiled food, omeprazole, and rifampicin.
Levels increased: amitriptyline, caffeine, clomipramine, diclofenac, diazepam, fluvoxamine, imipramine, nicergoline, phenacetin, quinolones, theophylline

References

Datta P, Rewers-Felkins K, Aurora N, *et al*. Estimation of riluzole levels in human milk and infant exposure during its use in a patient with ALS. *J Hum Lact* 2018;34:355–7.

Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012;3:CD001447.

National Institute for Health and Care Excellence (2001). *Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease*. NICE technology appraisal guidance TA20. Available at: 🖱 https://www.nice.org.uk/guidance/ta20.

Rituximab

Rituximab is a chimeric monoclonal antibody. It was initially developed in the 1990s as a treatment for non-Hodgkin's lymphoma. It was shown to be effective in rheumatoid arthritis in 2004 and is now used in a wide range of autoimmune neurological diseases.

Uses

Licensed uses

In the UK/USA

- Rituximab is licensed for the treatment of granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis with corticosteroids in individuals aged 18 years and older.

Off-label uses (not exhaustive)

- CANOMAD.
- IgM paraproteinaemic neuropathy with anti-MAG antibodies.
- Primary CNS vasculitis (refractory cases, chronic).

Primary CNS Lymphoma (first-line and refractory disease)

- LEMS (resistant cases, chronic).
- MG (refractory cases or early in MuSK positive cases, chronic).
- Neurolupus.
- NMO (first-line, chronic).
- PM/DM (refractory cases, chronic).
- Sjögren's syndrome.
- Stiff person syndrome (refractory cases).

Presentation

- *Trade names*: MabThera®, Rituxan®, Ruxience® and Truxima® Generics are not available.
- *Formulations*: rituximab is available as a concentrate for IV infusion and a solution for SC injection. Concentrate for IV infusion (10 mg/mL): 100 mg and 500 mg. Solution for SC infusion (1400 mg/11.7 mL): 1400 mg.

Mechanism of action

Rituximab is a chimeric mouse/human monoclonal antibody, which targets the CD20 antigen located on pre-B and mature B-cell lymphocytes. It depletes B cells by promoting apoptosis and mediating cell lysis through cell-mediated cytotoxicity.

Toxicity and side effects

- *Common—Dermatological*: alopecia. *Endocrine*: hypercholesterolaemia. *Gastrointestinal*: abdominal pain, diarrhoea, dyspepsia, gastroenteritis, and stomatitis. *Musculoskeletal*: arthralgia and myalgia. *Neurological*: dizziness, headache, and paraesthesiae. *Psychiatric*: anxiety and depression. *Respiratory*: respiratory tract infections.
- *Serious—Cardiovascular*: congestive heart failure and MI. *Dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis. *Haematological*: neutropenia. *Immunological*: hypersensitivity (including anaphylaxis), increased risk of infections, and infusion-related reactions. *Neurological*: PML.

Contraindications

- *Absolute*: hypersensitivity, active/severe infections, immunosuppression, severe heart failure, and uncontrolled cardiac disease.
- *Relative*: there are limited data on the use of rituximab in renal or hepatic impairment, but dose reductions are not required.

Use in special populations

- *Elderly*: no safety studies have specifically been conducted in this group. No dose reductions are required.
- *Pregnancy*: There is very limited data with regards fetal outcomes. Data that exists does not suggest an association with adverse pregnancy outcomes. Rituximab will not cross the placenta in the first trimester hence should not cause direct teratogenic effects. IgG immunoglobulins cross the placenta later in pregnancy and neonatal exposure is associated with depleted neonatal B cells. Infants exposed to rituximab *in utero* should not receive live vaccines until they are at least 6 months old. Rituximab should only be considered when benefits outweigh risks.
- *Lactation*: Due to the large size of the protein only a minimal amount is excreted in breastmilk with subsequent degradation in the infant gastrointestinal tract. The manufacturer recommends discontinuation during breastfeeding. The American College of Rheumatology have stated that given the infant's limited exposure, breastfeeding is acceptable.

Efficacy

See relevant conditions in Chapter 7, Other inflammatory disorders of the central nervous system.

Dosing and monitoring

Dosing

Dosing regimens differ, depending on the indication.

- *NMO*: treatment can be initiated using either two 1 g infusions of rituximab at an interval of 2 weeks or 4-weekly 375 mg/m^2 of BSA.
- *Granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis:* a weekly infusion of 375 mg/m^2 of BSA each week for 4 weeks.
- Initial doses should be given at a rate of 50 mg/h, and this can be increased at 50 mg/h increments every 30 min, until a maximum rate of 400 mg/h. Further infusions can be started at a rate of 100 mg/h and

increased at 100 mg/h increments every 30 min, until a maximum rate of 400 mg/h. Concurrent infusions of corticosteroids may be necessary to reduce infusion-related reactions. An antihistamine and analgesia should be given preceding the rituximab infusion.

Monitoring

Patients should be screened for hepatitis B, with hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing), prior to treatment initiation. The FBC should be measured before, and at regular intervals during treatment, given the risk of haematological cytopenias. All patients should be observed for infusion reactions and be given a patient alert card with each infusion. Clinical response to rituximab treatment is ideally assessed at 4–6 months after the first dose.

Pharmacokinetics and interactions

Pharmacokinetics

Immunoglobulins and their complexes are mostly broken down by the reticuloendothelial system. The half-life is ~21 days. The drug remains detectable in the serum at 6 months. B-cell recovery begins at ~24 weeks, with normalization of B-cell levels usually occurring at 1 year. A minority of patients have prolonged B-cell depletion lasting 2 years.

Interactions

Vaccines may be less effective during treatment and should be completed at least 4 weeks prior to therapy. Live vaccination should be avoided during treatment.

References

Sammaritano LR, Bermas BL, Chakravarty EE, *et al*. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020;72:529–56.

Rufinamide

Rufinamide was first marketed in the UK as an ASM in 2007. It is an orphan drug (drug used in rare conditions) that is only licensed for the treatment of Lennox–Gastaut syndrome. In practice, rufinamide is a second-line agent for this indication. Rufinamide may be particularly useful in individuals prone to atonic/drop attacks. Recent clinical trials have shown that there may be some extended benefit in focal-onset seizures; however, the effects in the initial clinical trials were marginal.

Uses

Licensed uses

In the UK/USA (licensing is the same)

- *Epilepsy*: rufinamide is licensed for the treatment as an adjunct of seizures associated with Lennon–Gastaut syndrome in individuals aged 1 year and older.

Off-label uses

- Focal-onset epilepsy and refractory myoclonic-astatic epilepsy (Doose syndrome).

Presentation

- *Trade names*: Banzel® and Inovelon®. Generics are not available.
- *Formulations*: Rufinamide is available as a film-coated tablet and an oral suspension. Film-coated tablet: 100 mg, 200 mg, and 400 mg. Oral suspension: 40 mg/mL. These are bioequivalent.

Mechanism of action

Rufinamide's main mechanism of action is thought to be by blocking voltage-gated sodium channels. This inhibits neuronal activity and hence the spread of cerebral epileptic discharges.

Toxicity and side effects

- *Common—Dermatological:* Acne and rash. *Endocrine:* Oligomenorrhoea. *Gastrointestinal*: Nausea and vomiting are the most common side effects. Abdominal pain, constipation, diarrhoea, dyspepsia, reduced appetite, and weight loss are also common. *Haematological:* leucopaenia. *Neurological*: Neurological side effects are usually dose-dependent and tolerance develops after a few months. Dizziness, headache, and fatigue are very common side effects. Abnormal coordination, hyperactivity, nystagmus, and tremor are common. *Ophthalmological:* Blurred and double vision. *Psychiatric:* Anxiety and insomnia. *Respiratory:* Influenza-like symptoms and pneumonia.
- *Serious— Cardiovascular:* Rufinamide has been demonstrated to shorten the QT interval, which may cause arrhythmia in predisposed patients with congenital short QT syndrome. *Immunological:* Antiepileptic hypersensitivity syndrome has been reported. *Neurological:* An increase in epileptic activity and even status epilepticus can be triggered in some individuals.

Contraindications

- *Absolute*: hypersensitivity to rufinamide, triazole derivatives, or any of their excipients. Rufinamide is contraindicated in congenital short QT syndrome and severe hepatic impairment.
- *Relative*: there is currently little data on which specific seizure types rufinamide can exacerbate. Studies have shown that the pharmacokinetics of a small dose of rufinamide: 400 mg are unchanged in severe renal impairment. However, rufinamide is predominantly excreted by the renal system; hence, caution and lower doses are still recommended in patients with renal impairment. Rufinamide also undergoes extensive hepatic metabolism, hence caution should be used in mild and moderate hepatic impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and may benefit from lower dosing regimens. They are

also more likely to be exposed to pharmacokinetic interactions with other co-prescribed medications.
- *Pregnancy*: animal studies have demonstrated teratogenic effects; however, there are as yet no studies in humans. There is no information available as to possible changes in rufinamide's pharmacokinetics during pregnancy.
- *Lactation*: it is not known whether rufinamide is present in human breast milk. It is potentially toxic to the infant and hence an alternative feeding method may be preferred.

Efficacy

A randomized placebo-controlled trial investigated the efficacy of rufinamide for the management of Lennox–Gastaut syndrome. It demonstrated that when used as an adjunct in a group of patients aged between 4 and 30 years of age the median percentage reduction in total seizure frequency was 32.7% with rufinamide compared to 11.7% with placebo. Tonic–clonic and tonic–atonic (drop attacks) seemed to be the most responsive seizure types. These findings have been corroborated by further open-label, uncontrolled studies carried out in Europe.

Dosing and monitoring

Dosing

Start treatment at 200 mg twice daily. Increase the dose in intervals of two or more days by 200 mg twice daily. Titrate to response up to a maximum of 1.2 g twice daily in individuals with a body weight of 50–70 kg; and up to a maximum of 1.6 g twice daily in individuals with a body weight >70 kg.

Monitoring

Hepatic and renal function should be assessed at baseline and yearly whilst on rufinamide. An ECG should be considered prior to starting treatment in patients at risk of short QT syndrome.

Therapeutic drug monitoring: Optimum seizure control when used in monotherapy occurs at plasma concentrations of 30–40 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The exact value of oral bioavailability has not been determined however it is known to be dose-dependent (i.e. bioavailability reduces at higher doses) and is increased by food co-ingestion. T_{max} is 6 h when taken with food and 8 h in the fasted state. A third of rufinamide is bound to plasma proteins, predominantly albumin. Rufinamide is mainly metabolized by hydrolysis to the inactive metabolite: CGP 47292 in the liver. Involvement of the cytochrome P450 system is minor. Autoinduction does not occur. 70% of CGP 47292 is excreted in urine along with a small amount (<5%) of un-metabolized drug. The rest is excreted in faeces. The plasma half-life in adults is 6–10 h; this is expected to be shorter in children and longer in females.

Interactions

See Table 24.61.

Table 24.61 Interactions of rufinamide

Medications which alter rufinamide plasma levels	Medications whose plasma levels are altered by rufinamide
Levels decreased: carbamazepine, phenobarbital, phenytoin, and primidone. Levels increased: valproate.	Levels decreased: carbamazepine, combined hormonal contraceptives, and hormone replacement therapy, lamotrigine. Levels increased: Phenobarbital and phenytoin.

References

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Wheless J, Conry J, Krauss G, *et al.* Safety and tolerability in children with epilepsy: a pooled analysis of 7 clinical studies. *J Child Neurol* 2009;24(12):1520–5.

Sodium phenylbutyrate/taurursodiol/ AMX0035

Sodium phenylbutyrate/taurursodiol (PB/TURSO) was approved by the FDA in 2022, however following a failed phase 3 trial it was removed from the market at time of printing. It has not been approved for use in the UK/ Europe.

Uses

Off-label uses

- Sodium phenylbutyrate/taurursodiol for the treatment of ALS in adults

Presentation

- *Trade names*: Relyvrio™. Generics are not available.
- *Formulations*: Sodium phenylbutyrate/taurursodiol is available in packets containing 3 g sodium phenylbutyrate and 1 g taurursodiol. Sodium phenylbutyrate.

Mechanism of action

The exact mechanism of PB/TURSO is not clearly elucidated in the treatment of ALS. Phenylbutryate is a pan-histone deacetylase (HDAC) inhibitor and acts as a small molecular chaperone that reduces endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). Accumulation of misfolded proteins in the ER leads to ER stress and UPR activation, which can trigger apoptosis. By assisting with protein folding, PB reduces ER stress and UPR overactivation, preventing cell death. TURSO is a Bax inhibitor that reduces apoptosis through inhibition of the mitochondrial apoptosis pathway. Bax is a pro-apoptotic protein that triggers cell death. TURSO binds to Bax and prevents it from forming pores in the mitochondrial membrane, reducing apoptosis.

Toxicity and side effects

- *Common*—Cardiac*: elevated BNP and cholesterol levels, and palpitations. *Gastrointestinal*: abdominal pain, diarrhoea, nausea (GI intolerance was most common in the first 3 weeks of treatment) and salivary hypersecretion. Respiratory: Upper respiratory tract infection. *Neurological:* Dizziness.
- TURSO is a bile acid. Disorders like pancreatic insufficiency, intestinal malabsorption, or other diseases that may alter the concentration of bile acids PB-TURSO may not be absorbed. Disorders that interfere with bile acid circulation may also increase the risk for GI intolerance and diarrhoea.
- PB/TURSO has a high salt content (464 mg per packet) and should be taken into consideration in patients sensitive to high salt consumption (e.g. heart failure, hypertension, renal impairment).

Contraindications

- None.

Uses in special populations

- *Elderly*: No overall differences in safety or effectiveness were observed between those patients 65 years of age and older and those <65 years of age.
- *Pregnancy*: No data is available from human studies. In animal studies, administration of sodium phenylbutyrate and taurursodiol to rats throughout pregnancy and lactation resulted in increased offspring mortality at all doses tested, which were less than or similar to the clinical doses.
- *Lactation*: No data is available from human studies. In animal studies, administration of sodium phenylbutyrate and taurursodiol to rats throughout pregnancy and lactation resulted in increased offspring mortality at all doses tested, which were less than or similar to the clinical doses.

Efficacy

Approval by the FDA was granted after an initial rejection, with subsequent review considering further analysis, the unmet need in ALS, as well as regulatory flexibility in light of the high mortality rate of ALS. The CENTAUR trial was a 24-week randomized, double-blind placebo-controlled phase 2 study with subsequent open-label extension. 137 patients were randomized 2:1 to receive either PB/TURSO (*n* = 89) or placebo (*n* = 48). Symptom onset of ALS patients was within the previous 18 months and SVC was over 60%. 71% of patients were taking riluzole and 34% were taking edaravone.

Edaravone was approved by the FDA during CENTAUR and participants were permitted to commence treatment mid-trial. There was a statistically significant difference in the rate of reduction in the ALSFRS-R total score from baseline to week 24 in treated patients compared to placebo ($p = 0.034$).

At time of printing the phase 3 PHOENIX trial showed that the primary endpoint was not met with no significant difference observed between participants treated with PB/TURSO (AMX0035) and placebo in ALSFRS-R total score change from baseline at Week 48 ($p = 0.667$). No significant difference was observed in the subset of participants who met the CENTAUR trial criteria. There were also no significant differences observed across secondary endpoints.

Dosing and monitoring

Dosing

One packet for oral suspension (3 g sodium phenylbutyrate and 1 g taurursodiol) once daily for 3 weeks. After 3 weeks, increase to 1 packet twice daily.

Monitoring

No specific therapeutic drug monitoring is recommended. Monitor for worsening diarrhoea. Patients with significant hepatic impairment, renal impairment, and heart failure were not included in CENTAUR and extra caution should be utilized in these groups.

Pharmacokinetics and interactions

Pharmacokinetics

Median Tmax for PB is 0.5 h and TURSO 4.5 h. High-fat meals reduce absorption (Cmax reduced by 76%) and exposure (AUC reduced by 54%) to PB. High-fat meals do not alter absorption of TURSO, but increase overall exposure (AUC increase by 39%). PB is 82% bound to plasma protein. TURSO is 98% protein-bound. The majority of administered PB (~80–100%) is excreted in the urine within 24 h as the conjugated product, phenylacetylglutamine.

In vitro PB/TURSO induces CYP1A2, CYP2B6, and CYP3A4, inhibits CYP2C8 and CYP2B6, and is a substrate of OATP1B3, MATE2-K, OAT3, and BSEP.

Interactions

No clinical interaction studies have been performed between PB/TURSO and other medicinal products.

References

Fels JA, Dash J, Leslie K, Manfredi G, Kawamata H. Effects of PB-TURSO on the transcriptional and metabolic landscape of sporadic ALS fibroblasts. *Ann Clin Transl Neurol* 2022;9(10):1551–64.

Paganoni S, Macklin EA, Hendrix S, *et al*. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. *N Engl J Med* 2020;383(10):919–30.

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Sodium oxybate (γ-hydroxybutyrate)

Sodium oxybate is a CNS depressant used in the management of narcolepsy. It is effective in reducing the incidence of cataplexy and excessive daytime sleepiness in this condition. Its use is limited, to some extent, by its side effect of respiratory depression and its potential as a drug of abuse when used in high doses.

Uses

Licensed uses

In the UK/USA

- *Narcolepsy*: sodium oxybate is licensed for the treatment of narcolepsy with cataplexy (and excessive daytime sleepiness in the USA) in individuals aged 18 years and older.

Off-label uses

Sodium oxybate has been used off-label in a wide range of conditions, including alcohol dependence, fibromyalgia, and headache disorders.

Presentation

- *Trade names*: Xyrem®. Generics are available.
- *Formulations*: sodium oxybate is available as an oral solution in 180 mL vials of 500 mg/mL concentration.

Mechanism of action

The exact mechanism of action of sodium oxybate is unclear. It is the salt of an endogenous compound γ-hydroxybutyrate, a metabolite of the neurotransmitter GABA. Hence it is believed to act at $GABA_b$ receptors on dopaminergic and noradrenergic neurons. The overall result is a CNS depressant effect. Clinically, this promotes delta-wave sleep, increasing stage 3 and 4 sleep, while reducing the frequency of sleep-onset REM periods.

Toxicity and side effects

The commonest side effects occurring in >10% are dizziness, headache, and nausea. γ-hydroxybutyrate also has well-documented dependence effects when used illicitly, although this is thought to occur at higher doses than used therapeutically. The presence of a withdrawal syndrome on terminating treatment is also unclear—some patients have reported rebound increases in cataplexy and a syndrome comprising headache, and psychotic and sleep disturbance, although there is no clear evidence of this in clinical trial data.

- *Common—Cardiovascular*: hypertension and palpitations. *Dermatological*: hyperhidrosis and rash. *ENT*: nasal congestion and vertigo. *Gastrointestinal*: abdominal pain, anorexia, diarrhoea, nausea, and vomiting. *Musculoskeletal*: arthralgia and myalgia. *Neurological*: dizziness, dysgeusia, fatigue, headache, impaired balance, and concentration, paraesthesiae, sedation, sleep paralysis, and tremor are common. *Ophthalmological*: blurred vision. *Psychiatric*: abnormal dreams, confusion, insomnia, mood disorders, and sleep-walking. *Respiratory*: dyspnoea and snoring.

- *Serious—Psychiatric*: psychosis and suicidality are uncommon. *Respiratory*: apnoea and respiratory depression, which are commoner in patients with pre-existing sleep-related breathing disorders.

Contraindications

- *Absolute*: concomitant use of sedative hypnotic agents, e.g. alcohol, barbiturates, benzodiazepines, and opiates. Porphyria, previous hypersensitivity reactions to sodium oxybate or its excipients, major depression, and patients with succinic semialdehyde dehydrogenase deficiency.
- *Relative*: patients with cardiovascular disorders such as heart failure and hypertension (due to the high sodium load of the formulation), epilepsy (an increase in seizure frequency has been reported), history of drug abuse, and pre-existing respiratory depression. The starting dose should be halved in hepatic impairment, and treatment should be used with caution in patients with renal impairment, due to the high sodium load.

Use in special populations

- *Elderly*: there are limited data in the elderly. The elderly have an age-related deterioration in their renal and hepatic function, and hence may benefit from lower dosing regimens. Co-prescription of other medications is also more likely in the elderly, and hence the risk of pharmacokinetic and pharmacodynamic interactions, particularly CNS depression, is increased.
- *Pregnancy*: animal studies and data from a small number of pregnant women suggest increased rates of spontaneous abortions in the first trimester. Teratogenicity has not been reported. Sodium oxybate should be avoided in pregnancy.
- *Lactation*: Sodium oxybate is present in breast milk. There is a lack of robust evidence to definitively state safety during lactation. A small study showed breast milk levels returned to baseline 10–16 hrs after the second dose. Breastfeeding should be withheld from the first dose to 4–6 hrs after the second dose to minimize infant consumption.

Efficacy

A recent systematic review and meta-analysis of the use of sodium oxybate in narcolepsy–cataplexy patients identified six suitable RCTs. All six trials demonstrated a reduction in cataplexy attacks in a dose-related manner vs. placebo. The mean difference was –8.5% (95% CI –15.3 to –1.6) (the commonest dose used was 9 g/night). In addition, the study showed that excessive daytime sleepiness was reduced, as measured by the maintenance of wakefulness test, demonstrating a mean difference of 5.18% (95% CI 2.59–7.78).

Dosing and monitoring

Dosing

The initial starting dose should be 4.5 g/night. This should be split into two 2.25 g doses, taken last thing before sleep and ~3 h before this. This can be increased in intervals of 1–2 weeks by 1.5 g, as required; this increase should be split over the two dosing times. The maximum recommended dose is 9 g/night (titration will need to be re-commenced if the medication has not been used for 2 weeks or more).

Monitoring

Patients with a diagnosis or risk factors for sleep-related breathing disorders should be carefully monitored throughout treatment. Snoring severity scales and nocturnal oximetry can be used to further investigate these patients.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability of sodium oxybate is ~88%. Peak plasma concentrations occur at 0.5–1.25 h post-dose. Peak plasma concentration and the time at which it is reached post-dose is reduced by 59% and increased to 0.75–2 h, respectively, with co-ingestion of a high-fat meal. Sodium oxybate is <1% protein-bound. Clearance is via biotransformation to carbon dioxide and water by γ-hydroxybutyrate dehydrogenase and the Krebs cycle. No active metabolites have been identified. Less than 5% of unchanged drug is present in the urine. The majority is expired as carbon dioxide. The elimination half-life is 0.5–1 h.

Interactions

See Table 24.62.

Table 24.62 Interactions of sodium oxybate

Medications which alter sodium oxybate plasma levels	Pharmacodynamic interactions
Levels increased: Sodium valproate	With alcohol, antipsychotics, barbiturates, benzodiazepines, opioids, TCAs: increased risk of CNS depression. With β-blockers, candesartan and other antihypertensives: increased risk of hypotension.

References

Alshaikh MK, Tricco AC, Tashkandi M, *et al*. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. *J Clin Sleep Med* 2012;8(4):451–8.

Bogan RK, Thorpy MJ, Dauvilliers Y, *et al*. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. *Sleep* 2021;44(3):zsaa206.

Swick TJ. Postnatal treatment of women with narcolepsy who choose to breastfeed-time for a re-appraisal? *Sleep Med* 2017;36:178–9.

Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med* 2005;6(5):415–21.

Temazepam

Temazepam was first marketed in the 1960s. It is primarily used as a hypnotic in the short-term treatment of insomnia. It is effective at reducing the time to sleep onset, maintaining sleep, and improving sleep quality. However, like with other benzodiazepines and benzodiazepine-like drugs, its use is limited by its potential for addiction and tolerance with longer-term use. It has a relatively short half-life, when compared to other benzodiazepines, which likely reduces the impact of the benzodiazepine side effect profile.

Uses

Licensed uses

In the UK

- *Insomnia*: temazepam is licensed as a short-term treatment of insomnia in instances where it is severe, disabling, or subjecting the individual to extreme distress, in individuals aged >18 years old.

In the USA

- *Insomnia*: temazepam is licensed for the short-term (usually 7–10 days) treatment of insomnia in individuals aged >18 years old.

Off-label uses

- None.

Presentation

- *Trade names*: Restoril®. Generics are available.
- *Formulations*: temazepam is available as an oral solution and a tablet. Oral solution: 300 mL vial (10 mg/5 mL). Tablet: 10 mg and 20 mg.

Mechanism of action

See Benzodiazepines, p. 352.

Toxicity and side effects

See Benzodiazepines, p. 352. Rebound insomnia on cessation of treatment can occur.

Contraindications

See Benzodiazepines, p. 352. Temazepam is also contraindicated in acute narrow-angle glaucoma.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function. Side effects, including behavioural changes, confusion, headache, falls, and respiratory depression, are also more common. They benefit from lower doses, i.e. 5 mg. This can be increased to 10–20 mg if insomnia is severe.
- *Pregnancy*: One study of 379 pregnancies exposed to temazepam in the first trimester have not shown an increased risk of fetal malformations. Neonates are at risk of flaccidity, respiratory depression, and withdrawal if used in the latter half of pregnancy or in labour. Use in pregnancy should be avoided unless benefits outweigh risks.
- *Lactation*: temazepam is present in small amounts in human breastmilk. The amount would not be expected to cause significant adverse effects in nursing infants/ If taken by nursing mothers, the infant should be monitored for respiratory depression, sedation, and withdrawal (if temazepam is abruptly discontinued).

Efficacy

A randomized, double-blind, placebo-controlled trial published in 1979 compared the action of temazepam 30 mg with placebo. The trial showed that temazepam resulted in a statistically significant improvement in sleep induction ($p < 0.05$). The actual time to fall asleep was a mean of 44 min with temazepam vs. 82 min with placebo. Total sleep length and number of nocturnal awakenings were also improved. One meta-analysis comparing the benzodiazepines temazepam, triazolam, and nitrazepam with the benzodiazepine agonists zaleplon, zolpidem, and zopiclone found no significant difference in subjective sleep quality or overall adverse effects between the drug groups. There are no RCTs comparing temazepam at the standard 10 mg with the newer Z-drugs.

Dosing and monitoring

Dosing

Start treatment at 10–20 mg before sleep. This can be increased to a maximum of 40 mg if insomnia is severe. Temazepam should be used for the shortest possible duration, certainly <4 weeks.

Monitoring

Not usually required. The elderly and those with hepatic impairment should be monitored for confusion.

Pharmacokinetics and interactions

Pharmacokinetics See Benzodiazepines, p. 352.

Interactions See Benzodiazepines, p. 352.

References

Ban L, West J, Gibson J, *et al*. First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. *PLoS One*;2014;9(6):e100996

Glass JR, Lanctôt KL, Herrman N, *et al*. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;331(7526):1169–73.

Heffron WA, Roth P. Double-blind evaluation of the safety and hypnotic efficacy of temazepam in insomniac outpatients. *Br J Clin Pharmacol* 1979;8(1):69–72.

Temozolomide

Temozolomide was first licensed for use in the late 1990s. It is a derivative of the alkylating agent dacarbazine. It has proven efficacy in the first-line treatment of glioblastoma and in the treatment of recurrence in other high-grade gliomas. As per most of the chemotherapeutic agents, its use is limited by its side effect profile, particularly myelosuppression.

Uses

Licensed uses

In the UK/USA

- *GBM*: temozolomide is licensed for use with radiotherapy in the treatment of newly diagnosed GBM; it may then be used as monotherapy alone in individuals aged 18 years and older.

In the UK

- *Malignant glioma*: temozolomide is licensed for the treatment of malignant glioma which recurs or progresses after first-line therapy in individuals aged 3 years and older.

In the USA

- *Anaplastic astrocytoma*: temozolomide is licensed for use in the treatment of refractory anaplastic astrocytoma following chemotherapy containing a nitrosourea and procarbazine, in individuals aged 18 years and older.

Off-label uses

- Other brain tumours, e.g. ependymoma, pituitary tumours.

Presentation

- *Trade names*: Temodal®, Temodar®, Temomedac®, and Temozolomide Hospira®. Generics are available.
- *Formulations*: temozolomide is available as a capsule in 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg doses, and as a powder for IV injection at 100 mg/vial.

Mechanism of action

Temozolomide is a prodrug. Its active metabolite monomethyl triazeno imidazole carboxamide (MTIC) is formed at physiological pH and acts as an alkylating agent inhibiting DNA replication.

Toxicity and side effects

- *Common—Dermatological*: alopecia, pruritus, and rash. *Endocrine*: adrenal hypercorticism and weight increase. *Gastrointestinal*: abdominal pain, anorexia, and gastrointestinal disturbance are common. *Musculoskeletal*: arthralgia and myalgia. *Respiratory*: PCP is common; hence prophylaxis is required. Viral respiratory tract infections are also common.
- *Serious—Haematological*: myelosuppression is common, and this can result in fatal aplastic anaemia. Myelodysplastic syndrome with development of secondary malignancies can also occur.

Contraindications

- *Absolute*: patients with previous hypersensitivity reactions to temozolomide, its excipients, or dacarbazine. Severe myelosuppression—prior to dosing, patients must have a platelet count $>100 \times 10^9/L$ and a neutrophil count $>1.5 \times 10^9/L$.
- *Relative*: caution should be taken in patients with severe hepatic or renal impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function, and hence may benefit from lower dosing regimens. There is an increased risk of neutropenia and thrombocytopenia in those aged over 70 years.

- *Pregnancy*: temozolomide is associated with fetal malformations in animal studies. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant. Men should avoid fathering a child during, and for 6 months following, treatment.
- *Lactation*: temozolomide levels within breast milk are unknown . Mothers should be advised to avoid breastfeeding. Breastfeeding should be withheld for at least 1 week following the last dose.

Efficacy

An RCT investigating the treatment of patients with newly diagnosed GBM demonstrated a significant increase in 2-year survival from 10.4% with radiotherapy alone to 26.5% with radiotherapy and temozolomide.

For recurrent high-grade gliomas, an RCT showed high-dose temozolomide for 5 days was more effective than low-dose temozolomide for 21 days, while there was no clear benefit when comparing temozolomide with a PCV regimen (the percentages of patients completing 9 months of treatment were 26% vs. 13% vs. 17%, respectively, for 5 days of high-dose temozolomide, 21 days of low-dose temozolomide, and a typical PCV regimen).

The CeTeG/NOA-09 was an open-label randomized phase 3 trial (n = 141) which showed temozolomide and lomustine may improve survival when compared to temozolomide standard chemoradiotherapy in GBM with methylated MGMT promoter status. Due to the small size of the trial the investigators advice caution in interpretation of their findings.

Dosing and monitoring

Dosing

The dosage of temozolomide varies, depending on the BSA, level of bone marrow depression, clinical indication, local protocols, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines.

- *Typical regime for high-grade glioma*: 75 mg/m² for 42 days, alongside focal radiotherapy, followed by six cycles of maintenance chemotherapy using doses of up to 150–200 mg/m², depending upon toxicity.
- *Typical regime for refractory anaplastic astrocytoma*: an initial dose of 150 mg/m² daily for 5 days of a 28-day cycle. The dose is adjusted in subsequent cycles, depending on toxicity. The optimum duration of therapy is unknown.

Monitoring

Prior to initiation of treatment, FBC, renal, and liver function should be assessed. Regular FBC monitoring during treatment is recommended.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability of temozolomide is nearly 100%. Peak plasma concentrations are reached in 0.9 h. Oral bioavailability is reduced and T_{max} prolonged by co-administration with food. Temozolomide is ~15% protein-bound. It rapidly crosses the blood–brain barrier and is present in the CSF at ~30% of plasma concentrations. Temozolomide has a short half-life of 1.8 h; it is spontaneously hydrolysed at physiological pH to MTIC and temozolomide acid metabolite. MTIC is further metabolized to 5-amino-imidazole-4-carboxamide, an intermediate in DNA synthesis, and methylhydrazine, an alkylating agent. By 7 days, 38% of the temozolomide radioactive dose is recovered, the majority in the urine and 0.8% in the faeces. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

Interactions

See Table 24.63.

Table 24.63 Interactions of temozolomide

Medications which alter temozolomide plasma levels	Pharmacodynamic interactions
Levels increased: valproate	With myelosuppressive agents: may increase the likelihood of myelosuppression

References

Brada M, Stenning S, Gabe R, *et al*. Temozolomide versus procarbazine, lomustine and vincristine in recurrent high-grade glioma. *J Clin Oncol* 2010;28(3):4601–8.

Hammond LA, Eckardt JR, Baker SD, *et al*. Phase I and pharmacokinetic study of temozolomide on a daily-for-5-days schedule in patients with advanced solid malignancies. *J Clin Oncol* 1999;17(8):2604–13.

Herrlinger U, Tzaridis T, Mack F, *et al*.; Neurooncology Working Group of the German Cancer Society. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. *Lancet* 2019;393(10172):678–88.

Stupp R, Mason WP, van den Bent MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *NEJM* 2005;352(10):987–96.

Teriflunomide

Teriflunomide is an oral disease-modifying agent used in the treatment of MS. It can be associated with hepatic impairment, requiring careful blood monitoring.

Uses

Licensed uses

In the UK/USA

- *MS*: teriflunomide is licensed for relapsing forms of MS including clinically isolated syndromes, RRMS, and active SPMS.

Off-label uses

None.

Presentation

- *Trade name*: Aubagio®. Generics are not available.
- *Formulations*: oral tablets: 7 mg and 14 mg.

Mechanism of action

Teriflunomide is a reversible inhibitor of dihydroorotate dehydrogenase, a mitochondrial protein used in pyrimidine synthesis. It prevents the proliferation of B and T lymphocytes. It may also alter cytokine production.

Toxicity and side effects

- *Common—Cardiovascular*: hypertension. *Dermatological*: acne, alopecia, rash, and tinea infection. *Gastrointestinal*: diarrhoea, gastroenteritis, nausea, and vomiting. *Genitourinary*: increased urinary frequency and UTI. *Gynaecological*: menorrhagia. *Immunological*: hypersensitivity. *Musculoskeletal*: myalgia. *Neurological*: paraesthesiae and peripheral neuropathy. *Psychiatric*: anxiety. *Respiratory*: bronchitis and upper respiratory tract infections.
- *Serious—gastrointestinal*: hepatic impairment and pancreatitis. *Haematological*: neutropenia. *Musculoskeletal*: rhabdomyolysis. *Respiratory*: interstitial lung disease.

Contraindications

- *Absolute*: hypersensitivity, severe hepatic or renal impairment (Child–Pugh class C), severe active infection, pre-existing immunodeficiency, any significant cytopenia, and severe hypoproteinaemia.
- *Relative*: no dose adjustment is required in mild to moderate hepatic or renal impairment, but close monitoring is advised.

Use in special populations

- *Elderly*: separate studies have not been conducted in the elderly; however, the elderly experience an age-related deterioration in hepatic and renal function; hence caution is advised.
- *Pregnancy*: Animal studies suggest an increased risk of teratogenicity. Small studies looking at post-marketing experience in pregnancy have shown outcomes consistent with the general population. Experts generally recommend teriflunomide should not be used during pregnancy or in men wishing to father a child. Teriflunomide can take up to 2 years to be eliminated from the body, so pregnancy should be avoided for 2 years after discontinuation of the drug. This time can be reduced to a few weeks by taking activated charcoal or colestyramine.
- *Lactation*: There is minimal published experience of use by nursing mothers. Given this most experts would recommend that patients should not breastfeed whilst taking teriflunomide.

Efficacy

In the TEMSO trial, the ARR was reduced to 0.37 in the teriflunomide 14 mg treatment group, compared to 0.54 in the placebo group (relative reduction in ARR of 31.5%). Disability progression sustained for 3 months, and 6 months was significantly reduced with teriflunomide treatment (20.2% of treated patients exhibited progression of disability sustained for 3 months, compared to 27.3% in the placebo group, and 13.8% of treated patients developed disability progression sustained at 6 months, compared to 18.7% with placebo). Teriflunomide treatment was associated with a 67% reduction in MRI total lesion volume and a 69% reduction in gadolinium-enhancing lesions, compared to placebo, after 2 years. The TOWER study showed similar results for the ARR, and disability progression sustained at 3 months, but no significant difference in disability progression sustained at 6 months. The TENERE study comparing teriflunomide to high-dose SC IFN-β1a showed no significant differences in terms of treatment failure due to adverse events or lack of efficacy after 12 months and an equivalent effect on ARR reduction.

Dosing and monitoring

Dosing

Teriflunomide is administered as a 14 mg tablet, once daily.

Monitoring

LFTs should be checked prior to drug initiation, and monthly for the first 6 months. The drug should be stopped if liver injury is suspected. FBC and a renal profile should also be checked before initiation and during therapy, given the risk of cytopenias and kidney injury. All patients should be screened for latent TB infection prior to initiation. Patients should be monitored for symptoms or signs of infection, peripheral neuropathy, skin reactions, and hypertension. An accelerated elimination procedure using colestyramine (8 g every 8 h for 11 days) or activated charcoal (50 g every 12 h for 11 days) should be considered to reverse adverse reactions, given the slow elimination of teriflunomide from plasma. Teriflunomide can act as both a cytochrome P450 inhibitor and inducer. It may decrease the INR of patients on warfarin, and this should therefore be monitored. The administration of live vaccines should be avoided during treatment.

Pharmacokinetics and interactions

Pharmacokinetics

Maximal plasma concentrations are reached 1–4 h following administration, with complete bioavailability, which is unaffected by food co-ingestion. The drug is extensively bound to plasma protein (>99%). The drug reaches steady-state concentration at ~3 months. It can be metabolized initially by hydrolysis or oxidation but is eliminated mainly through biliary excretion of unchanged drug. There is some renal excretion of metabolites. The median half-life is ~19 days.

Interactions

See Table 24.64.

Table 24.64 Interactions of teriflunomide

Medications whose plasma levels are altered by teriflunomide	Pharmacodynamic interactions
Decreased levels: colestyramine and rifampicin. Increased levels: cefaclor, oestrogens (including oral contraceptive pill), repaglinide, and rosuvastatin	Vaccinations: administration of live vaccines should be avoided With warfarin: can decrease the INR

References

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Confavreux C, O'Connor P, Comi G, *et al*.; TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13(3):247–56.

Vermersch P, Czlonkowska A, Grimaldi LM *et al*.; TENERE Trial Group. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomized, controlled phase 3 trial. *Mult Scler* 2014;20(6):705–16.

Tiagabine

Tiagabine was first marketed in the UK as an ASM in 1998. It is a narrow-spectrum ASM, used as an adjunct in focal-onset epilepsy. It is limited by its potential to aggravate absence seizures. It benefits from having few pharmacokinetic interactions.

Uses

Licensed uses

In the UK/USA

(Licensing is the same.)

- *Epilepsy*: tiagabine is licensed, as an adjunct, for the treatment of focal-onset seizures in individuals aged 12 years and older.

Off-label uses

- None.

Presentation

- *Trade names*: Gabitril®. Generics are available.
- *Formulations*: tiagabine is available as a film-coated or non-coated tablet in 5 mg, 10 mg, and 15 mg doses.

Mechanism of action

The main mechanism of action of tiagabine is thought to be mediated by enhancing the effects of GABA. It acts selectively to inhibit GABA transporter-1, thereby inhibiting GABA uptake at neurons and glia.

Toxicity and side effects

Visual disturbances similar to vigabatrin are a theoretical concern, due to similarities in their mechanisms of action (i.e. both elevate brain GABA concentrations), but have not been reported to date.

- *Common—Dermatological*: Bruising. *Gastrointestinal*: abdominal pain, diarrhoea, nausea, and vomiting. *Musculoskeletal*: muscle twitching. *Neurological*: ataxia, confusion, dizziness, speech disorder, and tremor. *Ophthalmological*: blurred vision. *Psychiatric*: aggression, depressed mood, difficulty concentrating, emotional lability, insomnia, and nervousness.
- *Serious—neurological*: encephalopathy and non-convulsive status epilepticus have been reported. *Psychiatric*: psychosis and suicidal ideation have been reported.

Contraindications

- *Absolute*: hypersensitivity to tiagabine or any of its excipients, and acute porphyria. Avoid in severe hepatic impairment.
- *Relative*: caution is advised in patients who have absence seizures as there is a risk of non-convulsive status epilepticus. Caution is also advised when used in individuals with a history of mood and psychotic disorders. In mild to moderate hepatic impairment, reduce the dose and/or prolong the dose interval. The dose does not need to be changed in individuals with renal impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their hepatic function and may benefit from lower dosing regimens.
- *Pregnancy*: animal studies have not demonstrated teratogenic effects; however, there are no studies in humans. There are no data available as to changes in tiagabine pharmacokinetics during pregnancy, although tiagabine is highly protein-bound, and hence changes should be expected. Use in pregnancy depends on whether the benefits outweigh the potential risks.
- *Lactation*: it is not known whether tiagabine is present in human breast milk. If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

Several meta-analyses have looked at the clinical efficacy of tiagabine. A Cochrane review including six RCTs concluded that tiagabine use had an overall risk ratio for a 50% or greater reduction in seizures vs. placebo of 3.16 (95% CI 1.97–5.07) for patients with drug-resistant focal-onset epilepsy. Further studies suggest it is less effective than topiramate and levetiracetam.

Dosing and monitoring

Dosing

Start treatment at 5–10 mg daily in two divided doses. Increase by 5–10 mg daily at weekly intervals. The normal maintenance dose depends on the presence of enzyme-inducing drugs. The normal maintenance dose is between 30 mg and 45 mg with enzyme-inducing drugs, and 15–30 mg without them, given in 2–3 divided doses.

Monitoring

Baseline FBC, liver, and renal function tests are recommended. These should then be repeated yearly.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 20–200 ng/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is ~90%; T_{max} is 0.5–2 h. T_{max}, but not total bioavailability, is reduced by food co-ingestion. Steady state occurs at 1–2 days. Tiagabine is >95% protein-bound, predominantly to plasma albumin. It undergoes extensive hepatic metabolism by enzymes, including the cytochrome P450 system. The metabolites are inactive. Autoinduction does not occur. The half-life of tiagabine as a monotherapy is 5–9 h. This is reduced to 2–4 h in the presence of enzyme-inducing AEDs. ~2% of tiagabine is excreted unchanged by the renal system. The majority of the metabolites (>60%) are excreted in the faeces, the rest in the urine.

Interactions

See Table 24.65.

Table 24.65 Interactions of tiagabine

Medications which alter tiagabine plasma levels	Medications whose plasma levels are altered by tiagabine
Levels decreased: carbamazepine, phenobarbital, phenytoin, pregabalin, and primidone Levels increased: naproxen, and salicylates	Levels decreased: valproate

References

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Lawden M. Vigabatrin, tiagabine, and visual fields. *J Neurol Neurosurg Psychiatry* 2003;74:286.

Tizanidine

Tizanidine is a hydantoin derivative with similar biochemistry to the α2-agonist clonidine. It was first used for the treatment of spasticity in the mid-1990s. It remains an effective first-line treatment for many patients with generalized spasticity of various aetiologies, although careful monitoring of BP and liver function is required.

Uses

Licensed uses

In the UK/USA

- *Spasticity*: tizanidine is licensed for the treatment of spasticity (in the UK, specifically spasticity secondary to MS, spinal cord injury, or disease) in individuals aged 18 years and older.

Off-label uses

- Rebound headaches due to analgesia withdrawal, regional musculoskeletal pain syndrome, refractory insomnia in spas tic quadriplegia, chronic migraine, chronic neck, and lower back pain.

Presentation

- *Trade name*: Zanaflex®. Generics are available.
- *Formulations*: tizanidine is available as a capsule and a tablet. Capsules: 2 mg, 4 mg, and 6 mg. Tablets: 2 mg and 4 mg.

Mechanism of action

Tizanidine is an α2-adrenergic agonist, which acts presynaptically, particularly at spinal interneurons, to cause a reduction in excitatory neurotransmitter release, and thus reduce the firing of spinal motor neurons.

Toxicity and side effects

- *Common—Cardiovascular*: bradycardia, hypotension. *Dermatological*: pruritus, rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, LFT derangement, xerostomia. *Musculoskeletal*: back pain. *Neurological*: dizziness, dyskinesia, myasthenia. Paraesthesiae, somnolence, speech disorder, weakness. *Ophthalmological*: blurred vision. *Psychiatric*: anxiety, depression, delusions, hallucinations. *Respiratory*: fever, flu-like illness.
- *Serious—Gastrointestinal*: fatal hepatotoxicity remains rare but has been reported.

Contraindications

- *Absolute*: hypersensitivity to tizanidine, significant hepatic impairment, and concurrent use of strong CYP1A2 inhibitors, i.e. ciprofloxacin and fluvoxamine.
- *Relative*: concurrent antihypertensive therapy. Other CYP1A2 inhibitors (fluoroquinolones, amiodarone, mexiletine, propafenone, verapamil, cimetidine, famotidine, oral contraceptives, aciclovir, and ticlopidine). Tizanidine should be used with caution and with slow up-titration of the dose in renal impairment (CrCl <25 mL/min). Use is not recommended in hepatic impairment.

Use in special populations

- *Elderly*: the elderly experience an age-related decline in hepatic and renal function; co-prescription of drugs, including antihypertensives, is also more common; hence tizanidine should be used with caution.
- *Pregnancy*: use in pregnancy is not recommended, due to observed teratogenicity in animal studies. There are limited human data.
- *Lactation*: tizanidine passes into breast milk in small quantities. There are limited human data and hence the manufacturer advises patients should not breastfeed whilst taking tizanidine.

Efficacy

There are a number of studies showing tizanidine to be superior to placebo for spasticity. A 2008 systematic review of 53 studies investigating the efficacy, pharmacokinetics, and tolerability of tizanidine (including several large multicentre RCTs from the UK and USA) concluded that tizanidine is at least as effective as baclofen in controlling spasticity secondary to MS or spinal cord injury and may be better tolerated. A 1998 meta-analysis of ten trials found tizanidine to be of comparable efficacy to baclofen and diazepam, with less muscle weakness and better overall tolerability.

Dosing and monitoring

Dosing

Start treatment at 2 mg at night, increasing in 2 mg/day increments every 3–4 days, up to a typical maintenance regime of 18–24 mg/day in three or four divided doses. The maximum daily dose is 36 mg.

Monitoring

LFTs should be performed at baseline and monthly thereafter for the first 4 months. Discontinue tizanidine if there is evidence of hepatic dysfunction.

Discontinuation

To minimize the risk of potentially serious rebound hypertension and tachycardia, tizanidine should be withdrawn slowly over a period of weeks, with regular monitoring of BP.

Pharmacokinetics and interactions

Pharmacokinetics

Tizanidine capsules and tablets have broadly similar pharmacokinetics when administered in the fasted state. There is extensive first-pass metabolism, resulting in 40% bioavailability. Time to peak plasma levels is 1 h. When taken with food, tablets have higher, and capsules lower, plasma bioavailability. Time to peak plasma levels may also be delayed. Metabolism is predominantly via hepatic CYP1A2 enzymes to pharmacologically inactive metabolites, which are mainly excreted in the urine. Elimination half-life is ~2.5 h.

Interactions

See Table 24.66.

Table 24.66 Interactions of tizanidine

Medications which alter tizanidine plasma levels	Pharmacodynamic interactions
Levels increased: CYP1A2 inhibitors, in particular ciprofloxacin and fluvoxamine (combination contraindicated)	With antihypertensives and MAOIs: tizanidine may enhance hypotension. With beta-blockers: tizanidine may intensify AV nodal blockade. With CNS depressants: enhanced sedative effect of tizanidine With mirtazapine, SNRIs, and TCAs: may reduce the antispasticity effect of tizanidine

References

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Groves L, Shellenberger MK, Davis CS. Tizanidine treatment of spasticity: a meta-analysis of controlled, double-blind, comparative studies with baclofen and diazepam. *Adv Ther* 1998;15(4):241–51.

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Tofersen

Tofersen is an antisense oligonucleotide specifically designed for individuals with ALS who have a SOD1 mutation. The SOD1 mutation is responsible for 10–20% of familial cases of ALS and 1–2% of sporadic ALS cases. Administration is by intrathecal injection and requires a series of three loading doses, given at 14-day intervals, followed by ongoing maintenance doses administered monthly. The FDA first approved it in 2023, under an accelerated approval scheme, based on reduction in plasma neurofilament light chain rather than clinical outcomes.

Licensed uses

In the USA (Not licensed for use in the UK)

- Tofersen is licensed for the treatment of ALS in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene, in individuals aged 18 years and older.

Off-label uses

- None

Presentation

- *Trade names*: Qalsody®. Generics are not available.
- *Formulations*: Tofersen is available as a single use vial containing 100 mg in 15 mL.

Mechanism of action

Tofersen is an antisense oligonucleotide, which binds to SOD1 mRNA, resulting in its degradation, and a reduction in SOD1 protein synthesis.

Toxicity and side effects

- *Common—Immunological:* pyrexia. *Musculoskeletal*: arthralgia and myalgia. *Neurological:* CSF pleocytosis, elevated CSF protein, and neuralgia.
- *Serious—Neurological:* Aseptic meningitis, myelitis, radiculitis, papilledema (secondary to elevated ICP). Treatment discontinuation was not needed in a majority of occurrences of these serious reactions within clinical trials, which were investigated and managed according to standard of care. Neurologic serious adverse events occurred in 7% of patients exposed to tofersen in clinical trials.

Contraindications

- *Absolute*: None.
- *Relative*: No dose adjustments are required in hepatic or renal impairment.

Use in special populations

- *Elderly*: no differences were noted between younger and older patients in clinical trials. No dose adjustment is required.
- *Pregnancy*: No data is available from animal or human studies. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: No data is available from animal or human studies. Tofersen is present in the milk of lactating mice following subcutaneous administration. Consider temporarily using an alternative method of feeding if nursing mothers use tofersen.

Efficacy

108 subjects with SOD1 ALS were randomized 1:2 (n = 36 placebo group and n = 72 tofersen group) in a phase 3, 28-week randomized, double-blind, placebo-controlled clinical study in patients 23 to 78 years of age with weakness attributable to ALS. Concomitant riluzole and/or edaravone use was permitted. The trial did not meet its primary functional endpoint and FDA approval was attained due to a reduction in the surrogate marker, serum neurofilament light (NfL). The tofersen group experienced less decline from baseline in the ALSFRS-r compared to placebo, but the results were not statistically significant: adjusted mean difference of 1.2 (95% CI –3.2, 5.5, $p = 0.97$).

Dosing and monitoring

Dosing

Prior to administering tofersen, remove ~10 mL of cerebrospinal fluid, and then administer 15 mL (100 mg) of tofersen by intrathecal injection. Administer the first three loading doses at 2-week intervals, and then continue to administer the maintenance dose of 100 mg every 28 days thereafter.

Monitoring

Routine monitoring is not required.

Pharmacokinetics and interactions

Pharmacokinetics

The maximum CSF trough concentration occurred at the third dose, which was the last dose of the loading period. There was little to no accumulation for CSF tofersen with monthly dosing after the loading phase. Tofersen is transferred from CSF into the systemic circulation, with median Tmax plasma values ranging from 2 to 6 h. There was no accumulation in plasma tofersen exposure following monthly maintenance dosing. Tofersen is expected to be metabolized through exonuclease (3'- and 5')-mediated hydrolysis and is not a substrate for, or inhibitor or inducer of CYP450 enzymes. The effective half-life in CSF is ~ 4 weeks.

Anti-drug antibodies (ADA) were present in 58.4% (n = 97) of study participants (transient in 14 and persistent in 83). These resulted in decreased plasma tofersen by 32%. Effects of ADA on CSF tofersen clearance are unknown.

Interactions

There are no clinically significant interactions.

References

Miller T, Cudkowicz M, Genge A, *et al.* Trial of antisense oligonucleotide tofersen for SOD1 ALS. *NEJM* 2022; 387(12):1099–110.

Peggion C, Scalcon V, Massimino M, *et al.* SOD1 in ALS: taking stock in pathogenic mechanisms and the role of glial and muscle cells. *Antioxidants (Basel)* 2022;11(4):614.

Topiramate

Topiramate was first marketed in the UK as an ASM in 1995. It is predominantly used in the management of headache and epilepsy. In epilepsy, it is a broad-spectrum ASM, which can be used in most seizure types.

Uses

Licensed uses

In the UK/USA

- *Epilepsy*: topiramate is licensed as a monotherapy for focal-onset seizures and primary generalized tonic–clonic seizures (UK: in individuals aged 6 years and older; USA: individuals aged 2 years and older). As an adjunct, it is licensed in the treatment of focal-onset seizures with or without secondary generalization, primary generalized tonic–clonic seizures, and seizures associated with LGS in individuals aged 2 years and older (UK and USA).
- *Migraine*: topiramate is licensed for the prophylaxis of migraine in individuals aged 16 years and older in the UK and aged 12 years and older in the USA.

Off-label uses

- Absence seizures, ET, idiopathic intracranial hypertension, MOH, and prophylactic treatment of all TACs.

Presentation

- *Trade names*: Topamax®. Generics are available.
- *Formulations*: topiramate is available as a capsule, a tablet, and Sprinkle® capsules. Capsule: 25 mg, 50 mg, 100 mg. Tablet: 25 mg, 50 mg, 100 mg, and 200 mg. Sprinkle® capsules: 15 mg, 25 mg, and 50 mg.

Mechanism of action

The exact mechanism of action of topiramate remains unclear. Several analgesic and antiepileptic actions have been proposed: (1) enhancement of GABA-mediated inhibition by a route distinct from benzodiazepines and barbiturates; (2) modulation of several different types of ion channel—it inhibits voltage-dependent sodium channels and L-type VGCCs, and it enhances the activity of potassium channels; and (3) weak carbonic anhydrase inhibitor activity.

Toxicity and side effects

Carbonic anhydrase inhibitors reduce intracellular pH, resulting in an increased incidence of hypokalaemia, metabolic acidosis, nephrolithiasis, paraesthesia, polydipsia, and polyuria.

- *Common—Dermatological*: alopecia, pruritus, and rash. *Gastrointestinal*: anorexia, changes in weight (loss is commoner than gain), diarrhoea, and nausea are the most common side effects. *Haematological*: anaemia. *Musculoskeletal*: arthralgia, muscular weakness, and myalgia. *Neurological*: confusion, dizziness, fatigue, and paraesthesia are the most common side effects. Cognitive impairment, dysarthria, dysgeusia, impaired coordination and memory, seizures, parasomnia, tremor, impaired hearing, and vertigo can also occur. *Ophthalmological*: blurred and double vision. *Psychiatric*: aggression, anxiety, depression, loss of libido, insomnia, and mood swings. *Respiratory*: dyspnoea, epistaxis, and rhinorrhea.
- *Serious—Dermatological*: Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Gastrointestinal*: hepatitis and pancreatitis can occur. *Haematological*: leukopenia, thrombocytopenia. *Immunological*: hypersensitivity reactions have been reported. *Ophthalmological*: there have been rare reports of topiramate triggering secondary angle-closure glaucoma. This usually happens within a month of treatment and may be associated with choroidal effusions, and lens or iris displacement. Specialist ophthalmological advice and withdrawal of topiramate as soon as possible is recommended. Uveitis is rare. *Psychiatric*: mania, psychosis, and suicide have been reported.

Contraindications

- *Absolute*: hypersensitivity to topiramate or its excipients.
- *Relative*: topiramate should be avoided in individuals at risk of metabolic acidosis, acute porphyria, and urinary calculi. Topiramate is renally excreted; hence if the eGFR is <60 mL/min/1.73 m^2, use with caution at a lower dose. If the eGFR is <30 mL/min/1.73 m^2, then use half of the normal dose. Caution and lower dosing regimens are advised in individuals with moderate-to-severe hepatic impairment, as topiramate undergoes extensive hepatic metabolism. Caution in women of childbearing potential if not using effective contraception.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal and hepatic function and may benefit from lower dosing regimens.
- *Pregnancy*: animal studies have demonstrated teratogenic effects. Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk for cleft lip and/or cleft palate (oral clefts) and for being small for gestational age (SGA). SGA has been

observed at all doses, but is more common at higher doses. During pregnancy, topiramate plasma levels can decrease by up to 40%. Use in pregnancy involves weighing up the potential benefits and side effects, patient should be fully educated about the risks of using the medication in pregnancy (see Anti-seizure medications in young women, p. 38).

- *Lactation*: breastfed infants of mothers medicated with topiramate experience plasma levels 9–17% of maternal levels. If used, infants should be monitored for potential side effects and switched to an alternative feeding regimen if these are identified.

Efficacy

- *Epilepsy*: the SANAD study, a large unblinded RCT conducted in the UK, suggested that, for the treatment of focal-onset epilepsy, the rate of 12-month remission with topiramate, lamotrigine, and carbamazepine was similar. However, lamotrigine performed significantly better than topiramate in terms of time to treatment discontinuation due to a milder side effect profile.
- *ET*: topiramate was the first oral medication to be studied in a large multicentre, double-blind, placebo-controlled trial of ET ($n = 208$). Patients with moderate-to-severe ET were given 24 weeks of treatment with a placebo or topiramate (average final dose 292 mg/day). There was a significant improvement in tremor rating scales of 29%, compared to 16% with placebo ($p < 0.001$), as well as in improvement in function and disability ($p = 0.001$). However, 40% of patients experienced side effects, leading to a high dropout rate from the trial.
- *Headache*: topiramate is recommended as a first-line migraine prophylactic agent in adults. A Cochrane review of six trials demonstrated that topiramate at a total dose of 100 mg or 200 mg per 24 h was consistently more effective than placebo in reducing headache frequency. In one trial, there was a 53% response rate in the topiramate group, significantly higher than 23% in the placebo group. Topiramate use in cluster headache and SUNCT has also been evaluated in open-label studies and has been shown to be effective in inducing remission in patients who have not responded to first-line prophylactic agents. Topiramate has also been shown in RCTs to reduce the frequency of headache days in MOH. In one study, it significantly reduced the number of headache days per month by 6.4, compared with 4.7 days for placebo.

Dosing and monitoring

Dosing

Start treatment at 25 mg once at night for 1 week. This can then be increased by 25–50 mg/day in 1- to 2-weekly intervals and should be given in two divided doses.

- *Epilepsy*: when used as monotherapy, initial dose 25 mg/day; increase dose in 25 mg increments at 1–2 weekly intervals, the normal maintenance dose is 100–200 mg in two divided doses. The recommended maximum is typically 400 mg/day, although higher doses have been used.

When used as an adjunct, the initial dose is 25–50 mg/day. Dose can be increased in 25 mg increments at 1–2 weekly intervals, the normal maintenance dose is 200–400 mg daily in two divided doses. The maximum recommended dose is 400 mg/day.

- *ET*: doses can be started at 25 mg once or twice a day and titrated up in weekly increments of 25 mg, as required/tolerated, to a maximum dose of 400 mg/day.
- *Headache*: in migraine, use a starting dose of 25 mg, which can be increased at 1–2 weekly intervals by 25–50 mg in divided doses. The usual dose is 100–200 mg/24 h. In cluster headache, a starting dose of 25 mg is used and this can be increased at 1–2 weekly intervals to 100 mg/day, although some patients may require 200 mg/day for optimal response. In SUNCT, studies have used doses of 50–300 mg, and, in MOH, doses of up to 200 mg are used.

Monitoring

FBC and LFTs are recommended at baseline, 2 months, and every 6 months thereafter, while treatment is continued. Patients should be monitored for cognitive side effects and mood disturbances.

Therapeutic drug monitoring

Plasma concentration for optimum seizure control, when used in monotherapy, in adults is 5–20 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

The oral bioavailability of topiramate is >80%. T_{max} is 2–3 h. Neither of these parameters are affected by food co-ingestion. Steady state is reached in 4–5 days. 15% of topiramate is protein-bound. Only ~20% of topiramate is hepatically metabolized, although this is increased in the presence of enzyme-inducing drugs to ~50%. Six metabolites are formed, none of which are pharmacologically active. Autoinduction does not occur. Over 80% of the topiramate dose is excreted via the renal system. Up to 60% of topiramate is excreted unchanged in the urine. The half-life in adults not on enzyme-inducing therapy is 20–30 h, and with enzyme-inducing therapy 10–15 h. In patients with moderate impaired renal clearance (Cr Cl 30–69) clearance was reduced by 42%, with patients with severe renal clearance (Cr Cl <30) clearance was reduced by 54%.

Interactions

See Table 24.67.

Table 24.67 Interactions of topiramate

Medications which alter topiramate plasma levels	Medications whose plasma levels are altered by topiramate	Pharmacodynamic interactions
Levels decreased: carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenobarbital, phenytoin, primidone, St John's wort, and valproate Levels increased: amitriptyline, lithium, metformin, propranolol, and sumatriptan	Levels decreased: digoxin, eslicarbazepine acetate, glibenclamide, pioglitazone, risperidone, sumatriptan, and valproate Levels increased: amitriptyline, haloperidol, hydrochlorothiazide, lithium, metformin, and phenytoin	With other carbonic anhydrase inhibitors and bicarbonate: there is an increased risk of renal calculi formation With levetiracetam: increased risk of weight loss With valproate: increased risk of encephalopathy

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Trientine dihydrochloride

Trientine dihydrochloride (triethylenetetramine) is a copper-chelating agent used in the management of WD. It was first marketed in the UK in 1985. Its main advantage over penicillamine is its better side effect profile. The risk of exacerbating neurological symptoms may be slightly higher with trientine than penicillamine.

Uses

Licensed uses

In the UK/USA (Licensing is the same.)

- *Inborn errors of metabolism*: trientine is licensed for the treatment of WD in individuals of all ages who are intolerant of D-penicillamine.

Off-label uses

- None.

Presentation

- *Trade names*: Trientine dihydrochloride: Cufence®, and Trientine dihydrochloride Tillomed. Trientine tetrahydrochloride: Cuprior®, Trientine hydrochloride: Syprine®.
- *Formulations*: trientine dihydrochloride is available as a capsule at doses of 200 mg, 250 mg, and 300 mg. Trientine tetrahydrochloride is available as a film-coated tablet at 150 mg. Take care when switching between formulations as the amount of trientine base may not be exactly equivalent.

Mechanism of action

WD is characterized by the accumulation of copper in the liver, brain, and other tissues. This occurs secondary to impaired function of ATP7B, an enzyme required to bind copper to caeruloplasmin, allowing the release of copper into the bloodstream. Trientine is a copper-chelating agent, which binds copper atoms and is subsequently excreted by the urinary tract, thereby reducing total systemic levels of copper.

Toxicity and side effects

- *Common—Dermatological*: rash. *Gastrointestinal*: nausea.
- *Serious—Gastrointestinal*: severe colitis and duodenitis have been reported. *Haematological*: anaemia (rarely). *Neurological*: dystonia and MG have been reported in marketed use. *Respiratory*: asthma and bronchitis.

Contraindications

- *Absolute*: hypersensitivity to trientine dihydrochloride.
- *Relative*: studies have not been performed in patients with hepatic or renal impairment; hence no guidance concerning dose adjustment can be recommended.

Use in special populations

- *Elderly*: there are no data on the safety and efficacy of trientine in patients above 65 years of age; use with caution.
- *Pregnancy*: trientine has been shown to be teratogenic in animal studies, but there are insufficient data regarding its safe use in pregnant women with WD. Its use in pregnancy should be done only after careful consideration of the benefits and risks of treatment.

- *Lactation*: Limited data suggests that trientine is not present in breast milk. Breastfed infants appear to have normal copper and zinc levels. Caution should be taken when given to nursing mothers.

Efficacy

Trientine is effective at treating neurological symptoms of WD but also carries a significant risk of provoking early neurological deterioration due to the increase of serum-free copper through mobilization of stored copper, which can cross the blood–brain-barrier. A multicentre, retrospective analysis of data on 380 patients with WD who were treated with D-penicillamine or trientine monotherapy showed similar clinical efficacies; ~55% of patients with either agent used as monotherapy showed neurologic improvement in their symptoms. Treatment with trientine had a lower rate of side effects requiring discontinuation, when compared to penicillamine, but neurologic deterioration occurred more frequently in patients who were given trientine first: ~2% ($n = 6/295$) with penicillamine vs. ~10% ($n = 4/38$) with trientine ($p = 0.018$).

A randomized, double-blind study investigated the efficacy and tolerability of treating 48 patients with a neurological presentation of WD with either trientine or tetrathiomolybdate. Trientine was better tolerated (4.3% of patients developed adverse effects, compared to 28% receiving tetrathiomolybdate), but it had a significantly higher rate of neurological deterioration, compared to tetrathiomolybdate (26% vs. 4%; $p < 0.05$).

Dosing and monitoring

Dosing

Start treatment at 750–1250 mg/day daily in 2–4 divided doses, given before food. This can be then adjusted up to a maximum of 2.4 g/day, depending on the biochemical and clinical response.

Monitoring

Monitoring with 24 h urinary copper analysis every 6–12 months should be undertaken. FBC should be regularly undertaken to look for the development of iron deficiency anaemia.

Pharmacokinetics and interactions

Pharmacokinetics

Data on the pharmacokinetics of trientine is limited. Trientine is predicted to have low oral bioavailability due to a high first-pass effect. T_{max} occurs at 0.5–6 h post-dose. Food co-ingestion reduces bioavailability further (by up to 50%) and delays T_{max} by an average of 2 h. Trientine is rapidly metabolized by acetylation and excreted in urine. The mean half-life is 4 h. A large proportion of trientine binds copper in the gastrointestinal tract and is excreted in faeces.

Interactions

See Table 24.68.

Table 24.68 Interactions of trientine dihydrochloride

Medications which alter trientine plasma levels	Medications whose plasma levels are altered by trientine
Levels decreased: zinc	Levels decreased: zinc and serum iron

References

Brewer GJ, Askari F, Lorincz MT, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Arch Neurol* 2006;63(4):521–7.

Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. *Lancet* 1982;20(1):643–7.

Unfractionated heparin

Unfractionated heparin is a parenteral anticoagulant that is used in a variety of clinical settings. It was first discovered in 1916 and marketed for clinical use in the 1930s.

Uses

Licensed uses

In the UK/USA

Unfractionated heparin is licensed for the treatment of deep vein thrombosis and pulmonary embolism in individuals of all ages in the UK, and the treatment of all forms of venous thrombosis in the USA.

Off-label uses

- None.

Presentation

- *Trade names*: widely available in generic form.
- *Formulations*: heparin is available as a concentrate for infusion or injection. Heparin sodium is available at the following doses: 1000 iu/mL in 1 mL, 5000 iu in 5 mL, 10 000 iu in 10 mL, and 20 000 iu in 20 mL ampoules.

Mechanism of action

Heparin is an anticoagulant that acts by inhibiting thrombin and potentiating the naturally occurring inhibitors of activated factor X (Xa).

Toxicity and side effects

- *Common—Dermatological*: alopecia, purpura, rash. *Endocrine*: hyperkalaemia, osteoporosis. *Gastrointestinal*: diarrhoea, nausea, vomiting. *Haematological*: anaemia, thrombocytopenia. *Immunological*: injection site reactions, fever. *Urological*: haematuria.
- *Serious—Dermatological*: skin necrosis. *Gastrointestinal*: gastrointestinal haemorrhage, rectal haemorrhage, haematemesis, pancreatitis, melaena. *Haematological*: heparin-induced thrombocytopenia, priapism. *Neurological*: intracranial haemorrhage. *Respiratory*: haemothorax.

Contraindications

- *Absolute*: hypersensitivity to heparin or its excipients, patients who consume large amounts of alcohol, active bleeding, haemophilia or other bleeding disorders, severe liver disease (including oesophageal varices), purpura, severe hypertension, active TB, or increased capillary permeability. Patients with present or previous thrombocytopenia. The rare occurrence of skin necrosis in patients receiving heparin contraindicates the further use of heparin either by SC or IV routes because of the risk of thrombocytopenia. Because of the risk of postoperative haemorrhage, heparin is contraindicated during surgery of the brain, spinal cord, and eye, in procedures at sites where there is a risk of bleeding, in patients who have had recent surgery, and in patients undergoing LP or regional anaesthetic block.
- *Relative*: those who are deemed to be at high risk of bleeding. In patients with advanced renal disease and mild to moderate renal impairment, a reduction in dosage may be necessary to reduce the risk of bleeding.

Use in special populations

- *Elderly*: no dosing adjustment is required in the elderly, although there is an increased risk of bleeding; hence heparin should be used with caution.
- *Pregnancy*: heparin is not contraindicated in pregnancy. Heparin does not cross the placenta. Haemorrhage may be a problem during pregnancy or after delivery.
- *Lactation*: as a result of its high molecular weight, it is not excreted in breast milk and hence can be used by nursing mothers.

Efficacy

- Cerebral sinus thrombosis (see Low-molecular-weight heparin, e.g. tinzaparin, p. 629).

Dosing and monitoring

Dosing

As the effects of heparin are short-lived, administration by IV infusion is preferable to intermittent IV injections. This should be given as a loading dose of 5000 units IV and a maintenance dose of 1000–2000 units/h by IV infusion (or by 5000–10 000 units 4-hourly IV injection).

Monitoring

Daily laboratory monitoring (ideally at the same time each day, starting 4–6 h after initiation of treatment) is essential during full-dose heparin treatment, with adjustment of the dosage to maintain an aPTT value 1.5–2.5 times midpoint of the normal range or control value. Platelet counts should be measured in patients receiving heparin treatment for longer than 5 days, and the treatment should be stopped immediately in those who develop thrombocytopenia.

Pharmacokinetics and interactions

Pharmacokinetics

After injection, heparin extensively binds to plasma proteins. Heparin is metabolized in the liver, and the inactive metabolic products are excreted in the urine. The half-life of heparin is dependent on the dose.

Interactions

See Table 24.69.

Table 24.69 Interactions of unfractionated heparin

Pharmacodynamic interactions
With antiplatelets, anticoagulants, dipyridamole, iloprost, NSAIDs: increased risk of bleeding
With nitrates: reduced anticoagulant effect of heparins.
With ACE inhibitors, angiotensin receptor II antagonists, and aliskiren: increased risk of hyperkalaemia

References

Coutinho J, de Bruijn SF, Deveber G, Stam J. Anticoagulation for cerebral venous sinus thrombosis. *Cochrane Database Syst Rev* 2011;8:CD002005.

Einhaupl K, Villringer A, Meister W, *et al*. Heparin treatment in sinus venous thrombosis. *Lancet* 1991;338(8767):597–600.

Valproate

Valproate was first marketed in the UK as an ASM in 1974. It is a broad-spectrum ASM, often used first-line in primary generalized seizures where no other ASM has been shown to be more effective (although others may have fewer side effects). It is thought to be less effective, when compared to carbamazepine, in focal-onset seizures. Its main disadvantages are its adverse effect profile, marked teratogenic potential, non-linear pharmacokinetics, and substantial drug interactions.

Uses

Licensed uses

In the UK

- *Epilepsy*: valproate is licensed as a monotherapy or as an adjunct for the treatment of any form of epilepsy in patients of any age.
- *Bipolar*: valproate is licensed for treatment of a manic episode in bipolar disorder when lithium is contraindicated or not tolerated.

In the USA

- *Epilepsy*: valproate is licensed as monotherapy and adjunctive therapy for the treatment of complex partial seizures occurring either in isolation or in association with other types of seizures and in the treatment of simple and complex absence seizures. It is also licensed

for use as an adjunct, but not as a monotherapy, for the treatment of patients with multiple seizure types, including absence seizures.
- *Migraine*: valproate is licensed for the prophylaxis of migraine in individuals aged 12 years and older.
- *Bipolar*: valproate is licensed for acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

Off-label uses

- Refractory status epilepticus and Sydenham's chorea.

Presentation

- *Trade names*: Convulex®, Depacon®, Depakene®, Depakote®, Dyzantil ®, Epilim®, Epilim Chrono®, Epilim Chronosphere®, Epilim IV®, Episenta®, Epival®, Stavzor®, and Syonell ®. Generics are available.
- *Formulations*: valproate is available as sodium valproate, valproate semisodium, and valproic acid. Valproic acid has a one-to-one dose relationship with sodium valproate. Valproate semisodium (Depakote®) is a compound of sodium valproate and valproic acid in a 1:1 molar relationship.
  1. Sodium valproate is available PO in both standard and modified-release formulations and as a powder and solution for IV injection. Standard-release formulations include a tablet, an enteric-coated tablet, an oral solution, a sprinkle capsule, and a solution for injection. Tablet: 100 mg. Enteric-coated tablet: 200 mg and 500 mg. Oral solution: 250 mg/5 mL. Sprinkle capsule: 125 mg. Solution for injection: 100 mg/mL in a 5 mL vial. Modified-release formulations include a capsule, granules, and a tablet. Capsule: 125 mg. Granules: 50 mg, 100 mg, 250 mg, 500 mg, and 750 mg. Tablet: 250 mg and 500 mg.
  2. Valproate semisodium is available as an enteric-coated tablet at doses of 250 mg and 500 mg.
  3. Valproic acid is available as enteric-coated tablets in doses of 150 mg, 300 mg, and 500 mg.

Mechanism of action

The dominant mechanism of action in epilepsy or migraine has not been conclusively established. Sodium valproate raises levels of GABA, possibly through inhibition of its metabolism (e.g. by inhibiting GABA transaminase). It has also been shown to reduce high-frequency neuronal activity, possibly by blockade of voltage-sensitive sodium channels or by activation of calcium-dependent potassium channels. This may reduce epileptic activity and cortical spreading depression present in migraine. In addition, valproate has been shown (*in vitro*) to reduce meningeal inflammatory infiltrate extravasation, a process which is thought to occur in migraine.

Toxicity and side effects

- *Common—dermatological*: patients commonly experience alopecia; although this is usually temporary. The hair may grow back curly. Nail disorders. *Endocrine*: dysmenorrhoea and hyponatraemia. *Gastrointestinal*: gingival hyperplasia, diarrhoea, gastritis, and nausea are common initially. Weight gain is common with long-term use. The main concern is hepatic dysfunction which can be severe, particularly in at-risk groups: young children <3 years old, patients with congenital defects in enzymes involved in the urea cycle, and individuals with seizure disorders associated with prominent learning impairment. Raised LFTs are common and usually transient. Unless severe or associated with a raised prothrombin time, continued monitoring of liver function, rather than discontinuing valproate treatment, is appropriate. *Haematological*: thrombocytopenia (usually dose-related) is common; monitor platelet counts over 100 000 without intervention. Anaemia is also common (macrocytic). *Neurological*: confusion, convulsion, deafness, extrapyramidal disorders (especially tremor), fatigue, headache, memory impairment, and nystagmus. *Psychiatric*: aggression and impaired attention.
- *Serious—cardiovascular*: vasculitis. *Dermatological*: rarely, angio-oedema, Stevens–Johnson syndrome, erythema multiforme, DRESS syndrome, and toxic epidermal necrolysis have been reported. *Gastrointestinal*: severe liver damage, including failure, and pancreatitis have been rarely reported. *Haematological*: leukopenia, pancytopenia. Rarely, bone marrow failure, myelodysplasia, and red cell aplasia can occur. *Immunological*: rarely SLE. *Neurological*: encephalopathy and coma can occur secondary to hyperammonemia.

Of note, less commonly, syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, PCOS, a reversible Fanconi syndrome, renal failure, and osteoporosis can develop with use of valproate.

Contraindications

- *Absolute*: active liver disease, personal or family history of severe hepatic impairment, hypersensitivity to valproate or its excipients, and acute porphyria.
- *Relative*: hepatic impairment, history of pancreatitis, suspected mitochondrial disorder, thrombocytopenia, suspected urea cycle disorders, women of childbearing potential who are not using effective contraception. The dose should be reduced at increasingly severe levels of renal impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their hepatic and renal function. They are also more likely to have pharmacokinetic interactions with other co-prescribed medications and are more commonly predisposed to side effects, including sedation and reduced nutritional intake, and hence lower dosing regimens are often appropriate.

- *Pregnancy*: sodium valproate has a marked teratogenic effect, including the risk of fetal neural tube defects. Use in pregnancy involves weighing up the potential benefits and side effects (see Anti-seizure medications in young women, p. 38). If the medication is continued, then high-strength folic acid should be given throughout pregnancy. Prophylactic vitamin K should be given to minimize bleeding risks. Valproate levels decrease markedly during pregnancy; hence, if treatment is to be continued, increases in the dose may be considered.
- *Lactation*: breastfed infants are exposed to serum valproate levels 4–12% of maternal levels. If valproate treatment is continued during breastfeeding, then infants should be monitored for adverse effects, including haematological effects, and, if these are identified, the infant should be switched to an alternative feeding regimen.

Efficacy

- *Epilepsy*: a large multicentre, unblinded RCT in 2007 (the SANAD study) looked at the comparative efficacy and tolerability of lamotrigine, valproate, and topiramate in generalized epilepsy. It found clear evidence that valproate was more effective than lamotrigine and more tolerable than topiramate, and hence should be considered first-line in the treatment of generalized epilepsy. In contrast, a multicentre, double-blind trial carried out in 1992 comparing the efficacy of valproate with carbamazepine in focal-onset epilepsy demonstrated that carbamazepine gave better long-term control of seizures and had fewer side effects than valproate. For discussion of valproate's use in status epilepticus, see Status epilepticus, pp. 41–5.
- *Migraine*: a Cochrane review of valproate in migraine prophylaxis found that patients were twice as likely to experience a ≥50% reduction in headache frequency with sodium valproate, compared to placebo.

Dosing and monitoring

Dosing

- For the treatment of all forms of epilepsy:
- *oral administration*:
  Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.
- *IV administration*, age >12 years: Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50–100 mcg/mL). No recommendation regarding

the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses. In convulsive status epilepticus, Valproate can be given as a loading dose of 40 mg/kg and infused at a rate of 10 mg/kg/min in adults (maximum dose 3000 mg).

- *Migraine*: The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. Based on clinical experience, some patients require doses up to 1.5 g/day for sufficient treatment response.

Monitoring

Liver function and FBC should be assessed at baseline, at 2 months, and 6-monthly thereafter. Platelet function tests should be considered prior to any significant surgical intervention. Vitamin D monitoring and DEXA scans should be considered in individuals considered at risk of osteoporosis. Weight should be monitored throughout treatment.

Therapeutic drug monitoring

Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 50–100 mg/L. In migraine, a level of between 21 and 50 micrograms/mL has been shown in one study to reduce the frequency of headache more than higher serum levels (50–100 micrograms/mL).

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is >90% for standard-release medications. Oral bioavailability is higher with enteric-coated and suspension formulations, than extended-release tablets. The doses of extended-release preparations need to be 10–20% greater than normal preparations to have equivalent bioavailability. Food co-ingestion prolongs T_{max} but does not affect bioavailability. T_{max} is 1.5 h with standard preparations and syrup, 3–7 h with enteric-coated and granular formulations, and longer with extended-release formulations. Valproate is 90% bound to plasma proteins (less in the elderly due to reduced albumin levels).

Valproate undergoes extensive hepatic metabolism to multiple metabolites via the cytochrome P450 enzyme system. Valproic acid glucuronide and 3-oxo-valproic acid constitute just over one-third of these metabolites each. Some of the minor metabolites are pharmacologically active at a similar level to valproate. Autoinduction does not occur. More than 97% of valproate is renally excreted, the majority as metabolites and ~3% as unchanged drug. In adults without co-prescription of enzyme inducers, the half-life is 12–16 h. With enzyme inducers, the half-life is 5–9 h in adults.

Interactions

See Table 24.70.

Table 24.70 Interactions of valproate

Medications which alter valproate plasma levels	Medications whose plasma levels are altered by valproate	Pharmacodynamic interactions
Levels decreased: acyclovir, amikacin, carbamazepine, carbapenems*, cisplatin, diflunasil, eslicarbazepine acetate, ethosuximide, lamotrigine, methotrexate, naproxen, oral contraceptives, panipenem, phenobarbital, phenytoin, primidone, rifampin, ritonavir, and topiramate Levels increased: acetylsalicylic acid, chlorpromazine, clobazam, felbamate, fluoxetine, isoniazid, sertraline, and stiripentol	Levels decreased: phenytoin and topiramate Levels increased: amitriptyline, aripiprazole, carbamazepine–epoxide metabolite of carbamazepine, clomipramine, chlorpromazine, diazepam, ethosuximide, felbamate, lamotrigine, lopinavir, lorazepam, midazolam, naproxen, nimodipine, nortriptyline, paroxetine, phenobarbital, rufinamide, and zidovudine	With clonazepam: may cause absence status With lithium: increased risk of lithium neurotoxicity With cisplatin: increased risk of thrombocytopenia and neutropenia With Topiramate: Increased risk of hyperammonemia and hypothermia

* As a result of the magnitude of the interaction between carbapenem antibiotics (e.g. ertapenem, imipenem, meropenem, and panipenem) and valproate whereby valproate plasma levels are decreased to almost non-detectable values, these drug combinations can be considered contraindicated.

References

Kinze S, Clauss M, Reuter U, *et al*. Valproic acid is effective in migraine porphylaxis at low serum levels: a prospective open-label study. *Headache* 2001;41(8):774–8.

Linde M, Mulleners WM, Chronicle EP, *et al*. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013;6:CD010611.

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Verapamil

Verapamil, a calcium channel blocker, is the first-line prophylactic agent for episodic and chronic cluster headache. Its efficacy for these indications was first established in the 1980s. It is given in significantly higher doses than for cardiovascular indications, and so patients are at particular risk of bradycardia and heart block.

Uses

Licensed uses

In the UK/USA (Licensing is the same.)

- It is licensed for the management of a range of cardiological disorders, including angina, arrhythmias, and hypertension. It is not licensed for the treatment of neurological disorders.

Off-label uses

- Prophylaxis of cluster headache and related disorders.
- IA use for the treatment of RCVS, and cerebral vasospasm secondary to subarachnoid haemorrhage.

Presentation

- *Trade names*: Calan®, Cordilox®, Verelan®, Zolvera®. Generics are available.
- *Formulations*: verapamil is available as an oral solution, and a standard tablet. Oral solution: 40 mg/5 mL. Standard tablet: 40 mg, 80 mg, 120 mg, and 160 mg. A solution for intravenous injection is available but is only intended for the acute management of supraventricular tachycardia and hence will not be discussed further.

Mechanism of action

Verapamil is a calcium channel blocker and has been shown to block P-type calcium channels in the rat striatum. It may also block N- and Q-type calcium channels. Verapamil may exert its predominant effect by inhibiting calcium channels in the hypothalamus, i.e. the site where cluster headaches are believed to originate. Verapamil also has inhibitory activity on potassium channels, particularly the HERG (human ether-a-go-go related gene) potassium channel, and part of its efficacy may rely on HERG potassium channel blockade in the CNS.

Toxicity and side effects

- *Common—Cardiovascular*: angina on abrupt withdrawal of treatment, ankle swelling, bradycardia, hypotension. *Gastrointestinal*: constipation, nausea, and vomiting.
- *Serious—Cardiovascular*: asystole, heart block, heart failure. *Dermatological*: Stevens–Johnson syndrome.

Contraindications

- *Absolute*: acute porphyria, bradycardia, hypotension (systolic BP <90mmHg), known hypersensitivity, second- and third-degree AV block (unless pacemaker *in situ*), severe left ventricular systolic dysfunction, sick sinus syndrome (unless pacemaker *in situ*), AF/atrial flutter with accessory pathway (e.g. Wolff–Parkinson–White syndrome).
- *Relative*: hypertrophic cardiomyopathy. In severe hepatic impairment, verapamil should be reduced to one-third of the normal dose, and titration should be done carefully, with close monitoring of the heart rate and rhythm. Careful monitoring should also be undertaken in renal impairment, as there are limited data on verapamil toxicity in renal disease.

Use in special populations

- *Elderly*: with increasing age, there is reduced clearance of verapamil, and so accumulation is more likely. This increases the risk of cardiovascular adverse effects, such as AV block and sinus bradycardia, so elderly patients on verapamil should be closely monitored with regular ECGs and careful dose titration.
- *Pregnancy*: verapamil crosses the placental barrier, and studies in rats have shown that verapamil can cause fetal death and delayed growth when given in levels toxic to the mother. There are case reports and small studies in humans have suggested use in pregnancy may be associated with upper gastrointestinal malformations and phalangeal malformations, but these have not been identified since in larger studies. Overall, there are limited data. Verapamil should only be used when benefits outweigh risks and ideally avoided in the first trimester.
- *Lactation*: verapamil has been detected in breast milk, but the amount is thought to be too small to be harmful to the infant.

Efficacy

In a double-blind, randomized, placebo-controlled trial of 30 patients with cluster headache, 12 of the 15 patients on verapamil experienced a >50% reduction in headache frequency after taking verapamil for 2 weeks. Half of these experienced a reduction in headache frequency within the first week of treatment, while, at the end of 2 weeks, four patients in the verapamil group were headache-free. None in the placebo group experienced a reduction in headache frequency. The dose of verapamil used was 120 mg tds, and side effects were minimal, with no test subject discontinuing treatment due to side effects.

There are no RCTs assessing the safety and efficacy of verapamil, in the context of neuroendovascular procedures. Due to its vasodilatory properties, verapamil has been extensively used IA for the treatment of cerebral vasospasm, in the context of subarachnoid haemorrhage. The vasodilatory effect is comparable between proximal versus distal vessels and does not seem to be affected by prior vasodilatory treatment.

Dosing and monitoring

Dosing

Cluster headache: Start treatment at 120–160 mg tds, with titration of 80 mg every 2 weeks. The dose needed for effective prophylaxis varies considerably between patients; the range is 240–960 mg. Some patients may require doses as high as 1200 mg.

Vasospasm: Verapamil has been successfully used IA in cases of RCVS (multiple treatments of 10–15 mg of IA verapamil over 5–10 min each time or 10 mg followed by prolonged continuous infusion). The ideal dosing regimen is yet to be determined, since relapsing and remitting vasospasm might ensue in some cases, requiring multiple doses.

Monitoring

Regular ECG monitoring is advised when increasing the dose of verapamil and also once established on a stable dose, due to the risk of AV block and bradycardia.

High-dose IA verapamil (>15 mg total dose) has been associated with increases in ICP, increases in cerebral tissue glucose levels and reductions in cerebral perfusion pressure, thereby warranting hemodynamic and ICP monitoring until 12 h post-administration.

Pharmacokinetics and interactions

Pharmacokinetics

Verapamil is well-absorbed from the gut but undergoes extensive first-pass metabolism, so only 10–30% of the oral dose is bioavailable. It is a racemic mixture composed of (R)-verapamil and (S)-verapamil. It reaches peak concentrations at 1–2 h. Verapamil is metabolized by the hepatic cytochrome P450 system, mainly by the enzyme CYP3A4, to less active metabolites, which are largely excreted by the kidneys. It is 90% plasma protein-bound. In single doses, the mean half-life is 2–8 h, and, with repeated dosing, this increases to 4.5–12 h. Metabolism is reduced in liver dysfunction, and the half-life can increase to 14–16 h.

Interactions

See Table 24.71.

Table 24.71 Interactions of verapamil

Medications which alter plasma levels of verapamil	Medications whose plasma levels are altered by verapamil	Pharmacodynamic interactions
Levels increased: atorvastatin, macrolide antibiotics, sirolimus. Levels decreased: cimetidine, rifampicin, phenobarbital, St John's wort	Levels increased: alcohol, carbamazepine, colchicine, ciclosporin, dabigatran, digoxin, ivabradine, lenalidomide, midazolam, simvastatin, sirolimus, theophylline	With antiarrhythmics: increased risk of myocardial depression and AV block With antihypertensives, e.g. α-blockers: risk of profound hypotension With β-blockers: increased risk of asystole With lithium: increased risk of neurotoxicity With inhalational anaesthetic agents: increased risk of myocardial depression

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Leone M, D'Amico D, Frediani F, *et al*. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurol* 2000;54(6):1382–5.

Vigabatrin

Vigabatrin (VGB) was first marketed in the UK as an ASM in 1989. It is a narrow-spectrum medication, predominantly used in the treatment of infantile spasms. Its use as a broader-spectrum agent in epilepsy is limited by its high incidence of visual field defects. These are considered acceptable in infantile spasms because of the limited number of effective options and potential benefits but are not acceptable in focal-onset epilepsy where safer alternative ASMs are readily available.

Uses

Licensed uses

In the UK

- *Epilepsy*: vigabatrin is licensed as a monotherapy for the treatment of infantile spasms. It is also licensed for use as an adjunct in the treatment of refractory focal-onset epilepsy with or without secondary generalization, which has not been controlled with all other suitable ASMs. Both indications are for individuals of all ages.

In the USA

- *Epilepsy*: vigabatrin is licensed as an adjunct for the treatment of refractory complex partial seizures in adults who have not adequately responded to alternative treatments and in whom the potential benefits outweigh the risk of visual loss. In addition, it is licensed as a monotherapy for the treatment of infantile spasms in children aged 1 month to 2 years old for whom the potential benefits outweigh the potential risk of visual loss.

Off-label uses

- None.

Presentation

- *Trade names*: Sabril® and Kigabeq ®. Generics are available.
- *Formulations*: vigabatrin is available as a film-coated tablet, soluble tablets, and a powder for oral solution. Film-coated tablet: 500 mg. Powder: 500 mg per packet. Soluble tablets 500mg and 100mg.

Mechanism of action

The mechanism of action of vigabatrin is irreversible inhibition of GABA transaminase, the enzyme responsible for the breakdown of GABA. This potentiates the inhibitory action of GABA within the CNS, reducing the spread of epileptic discharges.

Toxicity and side effects

- *Common—Gastrointestinal*: abdominal pain, nausea, and weight gain. *Neurological*: dizziness, fatigue, headache, impaired attention and memory, paraesthesiae, speech disorder, and tremor. *Ophthalmological*: blurry vision, visual field defects have been reported in up to a third of patients. The defects are typically a concentric constriction in both eyes, more prominent nasally than temporally. These defects occur months to years following initiation of treatment

and may be dose- and length of treatment-dependent. The majority of patients with these defects are asymptomatic and hence have to be monitored, using perimetry-based visual field techniques, regularly. The cause of these visual field defects is not clear. It may be as a result of an idiosyncratic drug reaction or an accumulation of vigabatrin in the retina. Subsequent optic neuritis and atrophy have been reported, and it is recommended that vigabatrin is discontinued when field defects are detected. *Psychiatric*: aggression, agitation, depression, excitation, nervousness, and paranoia.
- *Serious—Dermatological*: angio-oedema is rare. *Gastrointestinal*: rarely hepatitis. *Neurological*: encephalopathy optic neuritis. *Psychiatric*: reports of mania, psychosis, and suicide.

Contraindications

- *Absolute*: hypersensitivity to vigabatrin or its excipients, and pre-existing visual field defects.
- *Relative*: vigabatrin should not be used in certain types of epilepsy—it can aggravate absence seizures and induce an absence-type status epilepticus. It may also exaggerate myoclonic seizures. Caution should be taken if other retinotoxic drugs are prescribed and if there is a prior history of behavioural problems, depression, or psychosis. Reduced doses are required in moderate-to-severe renal impairment. No dose adjustment is required in hepatic impairment.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in their renal function and may benefit from lower dosing regimens.
- *Pregnancy*: Limited available data from case reports and cohort studies pertaining to vigabatrin use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, animal studies have demonstrated teratogenic effects. No information is available on pharmacokinetic changes of vigabatrin during pregnancy. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: Limited information indicates that maternal doses of vigabatrin up to 2000 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months. No studies have been performed to assess the level of vigabatrin in breastfed infants. Until more data is available, vigabatrin should only be used with careful monitoring during breastfeeding. If used, infants should be monitored for potential side effects, and, if these are identified, the infant should be switched to an alternative feeding regimen.

Efficacy

As an adjunct in focal-onset epilepsy, with or without secondary generalization, the proportion of patients experiencing a 50% or more reduction in seizure frequency was 48% vs. 26% for placebo in one double-blind, placebo-controlled trial. For infantile spasms, one double-blind, placebo-controlled trial showed patients treated with vigabatrin had a 78% reduction in spasms compared with 26% with placebo.

Dosing and monitoring

Dosing

- For the adjunctive treatment of focal-onset seizures, age >18 years: start treatment at 500–1000 mg/day in 1–2 divided doses for 1 week. Increase by 500 mg each week depending on response. The normal maintenance dose is 2–3 g daily in 1–2 divided doses. The maximum recommended dose is 3 g a day.
- For treatment of infantile spasms the initial daily dosing is 50 mg/kg/day given in two divided doses (25 mg/kg twice daily); subsequent dosing can be titrated by 25 mg/kg/day to 50 mg/kg/day increments every 3 days, up to a maximum of 150 mg/kg/day given in 2 divided doses (75 mg/kg twice daily).

Monitoring

Baseline FBC, and renal and liver function tests should be performed, and these should be monitored at least yearly. Visual field testing should be conducted at baseline and every 3 months while on therapy, and about 3–6 months after the discontinuation of therapy. Weight should also be monitored during treatment.

Therapeutic drug monitoring

Measurement of plasma levels may be useful in ascertaining compliance where doses of between 1 and 3 g/day would be expected to have plasma levels of 0.8–36 mg/L. It should be noted that vigabatrin continues to work long after the medication has been stopped, due to irreversible blockage of GABA transaminase.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is 60–80%. T_{max} is 1–2 h. Neither bioavailability nor T_{max} are affected by food co-ingestion. Steady state is reached in 1–2 days. Vigabatrin has 0% protein binding and undergoes no hepatic metabolism. ~100% is excreted unchanged by the renal system. The half-life in a healthy adult is 5–8 h; this is directly proportional to the eGFR.

Interactions

See Table 24.72.

Table 24.72 Interactions of vigabatrin

Medications which alter vigabatrin plasma levels	Medications whose plasma levels are altered by vigabatrin
Levels decreased: felbamate	Levels decreased: phenytoin and rufinamide Levels increased: Clonazepam

References

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Vincristine

Vincristine is one of a group of drugs known as the vinca alkaloids. It was first licensed for use in the 1960s, initially in the treatment of leukaemia, although its indications have subsequently expanded. Within the context of brain tumours, it is used with procarbazine and lomustine as PCV triple therapy. It has synergistic antineoplastic effects with these agents. Its main limitations are its peripheral neurotoxic effects. Its myelosuppressive effects are relatively mild, compared to other chemotherapeutic agents.

Uses

Licensed uses

In the UK

- *Haematological*: vincristine is licensed for use in malignant lymphomas, multiple myeloma, idiopathic thrombocytopenic purpura, and leukaemia in individuals of all ages.
- *Solid tumours*: vincristine is licensed for use in both paediatric and adult solid tumours.

In the USA

- *Haematological*: vincristine is licensed for use in the treatment of leukaemia and lymphoma.
- *Solid tumours*: vincristine is licensed for use in the treatment of neuroblastoma, rhabdomyosarcoma, and Wilms' tumours.

Off-label uses

- None

Presentation

- *Trade names*: Oncovin® and Vincasar PFS®. Generics are available.
- *Formulations*: vincristine is available as a solution for IV injection at concentrations of 1 mg/mL in 2 mL and 5 mL vials.

Mechanism of action

Vincristine inhibits neoplastic cell proliferation by binding to tubulin, thus preventing microtubule formation and stopping cell cycling during metaphase. It may also block glutamic acid utilization, thereby impairing protein synthesis. It is highly lipophilic but is thought to poorly penetrate the blood–brain barrier due to the presence of drug efflux pumps, e.g. P-glycoproteins, in healthy cerebral capillaries. The mechanism by which it enters the brain parenchyma and affects brain tumours is thus unclear but may be due to peritumoural disruption of the blood–brain barrier.

Toxicity and side effects

- *Common—Dermatological*: alopecia and rash. Injection site reactions—vincristine is a vesicant. *Gastrointestinal*: gastrointestinal disturbance, including abdominal pain, constipation, diarrhoea, and weight loss, can occur. *Haematological*: leucopenia (although, compared to other vinca alkaloids, vincristine causes negligible myelosuppression). *Ophthalmological*: transient cortical blindness.
- *Serious—Gastrointestinal*: impaction and intestinal obstruction. *Immunological*: anaphylaxis has been reported. *Neurological*: peripheral neuropathy can be dose-limiting—often starting with sensory impairment and paraesthesiae, progressing to neuropathic pain and motor difficulties. These may reduce with a reduction in dose but can persist. *Ophthalmological*: optic atrophy, leading to blindness, can occur. *Renal*: uric acid nephropathy. *Respiratory*: acute shortness of breath and severe bronchospasm.

It is often fatal if mistakenly given by the intrathecal route.

Contraindications

- *Absolute*: hypersensitivity to vincristine or its excipients, and patients with demyelinating variants of Charcot–Marie–Tooth disease.
- *Relative*: previous spinal irradiation or peripheral neurological disease may have an additive neurotoxic effect with vincristine. Vincristine undergoes hepatic metabolism; hence a 50% reduction in the dose is advised if bilirubin level is >51 micromol/L. No dose adjustment is required in renal disease.

Use in special populations

- *Elderly*: the elderly have an age-related deterioration in hepatic function, and hence liver function will need to be cautiously monitored. Elderly patients may also be more susceptible to both the urological and neurological adverse effects.
- *Pregnancy*: vincristine is teratogenic in humans. Women of childbearing age should be offered contraception and advised to avoid becoming pregnant.
- *Lactation*: vincristine levels within breast milk is unknown. Most sources recommend that it should not be used whilst breastfeeding.

Efficacy

Within the context of brain tumours, vincristine is usually administered as part of the PCV chemotherapy regimen (see Lomustine, p. 626 for further discussion of the evidence).

Vincristine appears to be effective in this regimen, even though it has well-documented low penetration across the blood–brain barrier. A meta-analysis of trials investigating the treatment of high-grade glioma, looking specifically at whether addition of vincristine to the chemotherapeutic regimen makes a difference to survival, demonstrated a statistically significant synergistic benefit of adding vincristine to procarbazine and lomustine.

Dosing and monitoring

Dosing

The dosage of vincristine varies, depending on the BSA, clinical indication, local protocols, individual toxicity, and other adjuvants used in the chemotherapy regimen. Readers are advised to follow local guidelines. Typical regimens use doses of 1.4–1.5 mg/m^2, with a maximum dose of 2 mg/week.

Monitoring

Prior to initiation of treatment, FBC, and renal and liver function should be assessed. An FBC should be repeated regularly during therapy.

Pharmacokinetics and interactions

Pharmacokinetics

Vincristine has very poor oral bioavailability and hence needs to be administered by IV infusion. Its pharmacokinetics have a triphasic serum decay pattern, with half-lives at 5 min, 2.3 h, and 85 h. Terminal half-life can be between 19 h and 155 h in humans. Over 90% distributes from serum to tissue within 30 min. Metabolism is mediated primarily hepatically by the CYP3A system. 80% of the injected drug is ultimately excreted in the faeces, and the rest in the urine.

Interactions

See Table 24.73.

Table 24.73 Interactions of vincristine

Medications which alter vincristine plasma levels	Medications whose plasma levels are altered by vincristine	Pharmacodynamic interactions
Levels decreased: agents that increase the CYP3A subfamily of cytochrome P450 activity, e.g. bosentan, anticonvulsants, reverse transcriptase inhibitors. Levels increased: agents that inhibit the CYP3A, e.g. itraconazole, protease inhibitors, macrolide antibiotics	Levels decreased: phenytoin	With allopurinol, pyridoxine, and isoniazid: may increase the incidence of myelosuppression

References

Van den Bent MJ, Brandes AA, Taphorn MJ, *et al*. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013;31(3):344–50.

Van den Bent MJ, Carpentier AF, Brandes AA, *et al*. Adjuvant procarbazine, lomustine and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomised EORTC phase III trial. *J Clin Oncol* 2006;24(18):2715–22.

Warfarin

Warfarin is an oral coumarin anticoagulant that is widely used in the prevention of thrombosis and treatment of thromboembolic disease.

Uses

Licensed uses

In the UK/USA

- *Prevention of stroke*: warfarin is licensed for prophylaxis of systemic embolization in patients considered to be at risk of cardio-embolic stroke from AF, metallic heart valves, and ischaemic or rheumatic heart disease in individuals of all ages.
- *Treatment of venous thrombosis*: warfarin is also licensed for the treatment of venous thrombosis in individuals of all ages.

Off-label uses

- Cryptogenic stroke.

Presentation

- *Trade names*: Coumadin®, Marevan®, and Jantoven®. Generics are available.
- *Formulations*: warfarin is available as a hard tablet and a powder for reconstitution and IV injection (USA). Hard tablet: 0.5 mg, 1 mg, 2 mg (USA), 2.5 mg (USA), 3 mg, 4 mg (USA), 5 mg, 6 mg (USA), 7.5 mg (USA), and 10 mg (USA). Powder for injection: 5 mg vial.

Mechanism of action

Warfarin is a synthetic coumarin anticoagulant. It acts by inhibiting the formation of active clotting factors II, VII, IX, and X, as well as the anticoagulant proteins C, S, and Z. The precursors of these factors require the carboxylation of their glutamic acid residues by γ-carboxy glutamic acid to allow the coagulation factors to bind to phospholipid surfaces on the vascular endothelium. This reaction requires reduced vitamin K and is catalysed by γ-glutamyl carboxylase; the carboxylation is coupled to the oxidation of vitamin K to its epoxide. Vitamin K epoxide is reduced to vitamin K by vitamin K epoxide reductase complex-1 (VKORC-1). Warfarin directly inhibits VKORC-1, resulting in the synthesis of partially decarboxylated coagulation factors, with markedly impaired coagulant activity.

Toxicity and side effects

- *Common—Dermatological*: purpura, rash. *Gastrointestinal*: diarrhoea, jaundice, nausea, and vomiting.
- *Serious—Dermatological*: skin necrosis. *Gastrointestinal*: gastrointestinal haemorrhage, pancreatitis. *Haematological*: anaemia, epistaxis, thrombocytopenia. *Immunological*: allergic reaction. *Neurological*: intracranial haemorrhage. *Respiratory*: haemothorax. *Urological*: haematuria.

Contraindications

- *Absolute*: known hypersensitivity to warfarin or any of its excipients. Haemorrhagic stroke, clinically significant bleeding, within 72 h of major surgery with risk of severe bleeding, within 48 h post-partum, pregnancy, and drugs where interactions may lead to a significantly increased risk of bleeding.
- *Relative*: ischaemic stroke—in patients with AF, long-term treatment with warfarin is beneficial, but the risk of early recurrent embolism is low, and therefore a break in treatment after ischaemic stroke is justified to reduce the risk of haemorrhagic conversion. Warfarin treatment should be restarted 2–14 days following ischaemic stroke, depending on the size of the infarct and BP. In patients with large embolic strokes or uncontrolled hypertension, warfarin treatment should be stopped for 14 days. The INR should be measured more frequently in patients with hepatic or renal disease.

Use in special populations

- *Elderly*: the elderly are more at risk of bleeding, due to a combination of higher levels of hepatic impairment, renal impairment, falls, hypertension, and concomitant use of drugs which may alter INR levels. This group should have their INR monitored more frequently.
- *Pregnancy*: warfarin is teratogenic in the first trimester. There is also an increased risk of placental, fetal, and neonatal haemorrhage, particularly when used in the final weeks of gestation and at delivery. Hence warfarin shoud be avoided in pregnancy, particularly in the first and third trimesters.
- *Lactation*: warfarin is not present in milk in significant amounts and hence is considered safe for use by nursing mothers.

Efficacy

AF and Stroke: In the context of prevention of cardio-embolic stroke secondary to AF, numerous trials (SPAF-I, SPAF-II, SPAF-III, AFASAK, BAATAF, SPINAF, and CAFA) have demonstrated a two-third relative risk reduction of stroke in patients treated with dose-adjusted warfarin, compared to placebo, and a 39% relative risk reduction of stroke in patients treated with warfarin, compared to antiplatelet agents. The risk of major bleeding in patients on warfarin varies from 1.3% to 7.2% per year, depending on the population studied.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) found no significant difference between aspirin and warfarin in preventing recurrent ischaemic stroke amongst noncardioembolic and cryptogenic stroke. Although post-hoc analyses showed better outcomes in the warfarin arm in mild stroke severity (NIHSS ≤5), posterior circulation stroke sparing brainstem, those without hypertension at baseline, and in those with elevated NT-proBNP (often associated with cardiac dysfunction).

Cerebral Venous Sinus Thrombosis: The RE-SPECT CVT trial was a randomized prospective open-label study which assessed the safety and efficacy of dabigatran (150 mg bd) or warfarin (dose-adjusted to INR 2–3) in CVST (n = 120). No recurrent VTEs were observed, recanalization was noted in 67% of the warfarin-treated arm (95% CI, 52.9–79.7) and 60% in the dabigatran arm (95% CI, 45.9–73.0).

Dosing and monitoring

Dosing

Induction dose varies, depending on the age and indication. Follow local protocols. A typical induction dose is 5–10 mg daily for 2 days, with subsequent doses calculated depending on INR levels.

Monitoring

INR levels should be tested at regular intervals. Once the maintenance dose is established, it is rarely necessary to alter it. Those at high risk of bleeding benefit from more frequent INR monitoring. The target INR for most patients is 2–3 for the prevention of stroke in AF and for the treatment of venous thrombosis.

Pharmacokinetics and interactions

Pharmacokinetics

Warfarin is completely absorbed from the gastrointestinal tract. T_{max} is reached in ~4 h. ~99% of the drug is bound to plasma proteins. Its effective plasma half-life is highly variable and ranges from 20 h to 60 h; the terminal half-life is ~7 days. It is metabolized by the liver, and 92% is excreted in the urine, mainly as metabolites. In the liver, it is metabolized by various CYP isoenzymes, including CYP 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4.

Interactions

See Table 24.74.

Table 24.74 Interactions of warfarin

Medications which alter warfarin plasma levels	Pharmacodynamic interactions
Levels decreased: CYP2C9 inhibitors, e.g. carbamazepine, phenytoin. CYP1A2 inhibitors, e.g. omeprazole, phenytoin. CYP3A4 inhibitors, e.g. carbamazepine and phenytoin	With anticoagulants, antiplatelets, NSAIDs: increased risk of haemorrhage
Levels increased: CYP2C9 inhibitors, e.g. amiodarone and fluconazole; CYP1A2 inhbitors, e.g. aciclovir, oral contraceptives, and verapamil; CYP3A4 inhibitors, e.g. amlodipine, cimetidine, and ranitidine	With alcohol: variation in alcohol intake can affect anticoagulant control. With sulfonylureas: coumarins possibly enhance hypoglycaemia

References

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Zinc acetate

Zinc acetate is used in the treatment of WD. Its relatively safe side effect profile and low cost have meant it is often considered the preferred long-term maintenance therapy for WD.

Uses

Licensed uses

In the UK/USA

- *Inborn errors of metabolism*: zinc acetate is licensed for the treatment of WD in individuals of all ages. In the USA, it is only licensed as maintenance therapy after initial treatment with a chelating agent.

Off-label uses

- None.

Presentation

- *Trade names*: Galzin® and Wilzin®. Generics are not available.
- *Formulations*: zinc acetate is available in 25 mg and 50 mg capsules.

Mechanism of action

WD is characterized by the accumulation of copper in the liver, brain, and other tissues. This occurs secondary to impaired function of ATP7B, an enzyme required to bind copper to caeruloplasmin, allowing the release of copper into the bloodstream. Zinc salts induce enterocyte and hepatocyte metallothionein, a protein which binds to copper atoms with high affinity. Copper binding in enterocytes prevents absorption of copper from food and reabsorption of copper from bile and other gastrointestinal secretions. Copper is then trapped in the enterocytes and eventually lost during desquamation. The induction of hepatic metallothionein may have an additional beneficial effect by sequestering body copper in a non-toxic hepatic pool.

Toxicity and side effects

- *Common—Gastrointestinal*: abdominal discomfort (10% of patients); this side effect may be reduced if the dose is taken with some protein or if the first dose is delayed to mid-morning. It is common for serum amylase, lipase, and ALP to be mildly elevated in the first few weeks of treatment.
- *Serious—Haematological*: leucopenia, sideroblastic anaemia (both uncommon); likely to occur because of bone marrow suppression which may have resulted from copper deficiency.

Contraindications

- *Absolute*: hypersensitivity to zinc acetate.
- *Relative*: caution should be taken when treating patients with portal hypertension, as there is a risk of hepatic decompensation when switching from a copper-chelating agent. No dose adjustment is necessary in patients with renal impairment.

Use in special populations

- *Elderly*: there are no data on the safety and efficacy of zinc acetate in patients above 65 years of age; use with caution.
- *Pregnancy*: limited data from animal studies show no harmful effects of zinc acetate treatment in pregnancy. There are no controlled studies in humans. The dose of zinc acetate should be reduced to 25 mg tds and further adjusted, according to serum copper concentration and urinary copper excretion. Over-treatment may cause copper deficiency and may be especially harmful to the neonate, as copper is required for normal growth and mental development.
- *Lactation*: zinc is present in breast milk and should be avoided, if possible, as it could cause zinc-induced copper deficiency in the infant.

Efficacy

There are no multicentre prospective RCTs to estimate the efficacy of zinc monotherapy in WD. Generally, zinc acetate is given as maintenance therapy in symptomatic patients already treated with a chelating agent or in asymptomatic patients. A systematic review of one RCT and 12 observational studies of low validity suggested that zinc acetate monotherapy had a clinical efficacy similar to that of penicillamine in treating patients with WD who were asymptomatic or had neurological symptoms. 90% of patients on zinc acetate treatment had favourable clinical outcomes (remained asymptomatic or improved). In a single-centre randomized trial (included in the systematic review), 81% of patients receiving zinc acetate as the initial therapy showed favourable clinical outcomes. In another prospective study, 13 pre-symptomatic patients with WD were successfully treated with zinc acetate, and, over the follow-up period (3–9 years), none of them developed symptoms related to WD. Furthermore, zinc acetate monotherapy seems to be a better initial treatment choice than penicillamine in asymptomatic patients with WD or those with neurological symptoms. Zinc acetate treatment has a milder side effect profile, and there is a lower risk of initial neurological deterioration, when compared to penicillamine therapy.

Dosing and monitoring

Dosing

Zinc acetate has a slow onset of action; hence, in symptomatic patients, it is usually used either after copper detoxification with a chelating agent or as an adjunct with a chelating agent. It can be used as monotherapy in asymptomatic patients. Start treatment at 50 mg tds. This dose can be adjusted, according to biochemical and clinical response, up to a maximum of 50 mg five times daily.

Monitoring

Monitoring for anaemia, leucopenia, and decreased high-density lipoprotein (HDL) cholesterol levels should be undertaken (early manifestations of copper deficiency). Monitoring with 24 h urinary copper analysis every 6–12 months should be undertaken to ensure biochemical effectiveness. Measurements of urinary and/or plasma zinc may be useful in monitoring treatment compliance.

Pharmacokinetics and interactions

Pharmacokinetics

Pharmacokinetic evaluations based on zinc levels in blood are not useful, as its major site of action is the enterocyte. It is eliminated primarily in faeces.

Interactions

See Table 24.75

Table 24.75 Interactions of zinc acetate

Medications which alter zinc plasma levels	Medications whose plasma levels are altered by zinc
Levels decreased: oral iron, penicillamine, and trientine	Levels decreased: ciprofloxacin, levofloxacin, moxifloxacin, penicillamine, tetracyclines, and trientine

References

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Zonisamide

Zonisamide was first marketed in the UK as an ASM in 2005. It is a broad-spectrum drug, which can be used in both generalized epilepsies and focal-onset epilepsy. It benefits from having few pharmacokinetic interactions but is limited by its side effect profile.

Uses

Licensed uses

In the UK

- *Epilepsy*: zonisamide is licensed as an adjunct or a monotherapy for the treatment of focal-onset seizures with or without secondary generalization in individuals aged 18 years and older.

In the USA

- *Epilepsy*: zonisamide is licensed for the treatment as an adjunct of focal-onset seizures in individuals aged 18 years and older.

Off-label uses

- Absence seizures, chronic migraine, ET, motor fluctuations in PD, and myoclonus-dystonia.

Presentation

- *Trade names*: Zonegran®. Generics are available.
- *Formulations*: zonisamide is available as a capsule at doses of 25 mg, 50 mg, and 100 mg.

Mechanism of action

Epilepsy: The mechanism of drug action has not been fully established. *In vitro* studies have shown it modulates GABA-mediated inhibition of neurons. In addition, it blocks voltage-sensitive calcium and sodium channels, thereby suppressing neuronal firing. It also acts as a carbonic anhydrase inhibitor.

PD: There are several proposed mechanisms for the efficacy of zoninsamide in PD. (1) Inhibition of monoamine oxidase B (MAO-B). (2) Blockage of T-type calcium channels. (3) Modulation of levodopa-dopamine metabolism in the striatum. (4) Modulating receptor expression in the striatum.

Toxicity and side effects

Carbonic anhydrase inhibitors reduce intracellular pH, resulting in an increased incidence of hypokalaemia, metabolic acidosis, nephrolithiasis, paraesthesiae, polydipsia, and polyuria.

Common—Dermatological: alopecia, pruritus, and rash. *Gastrointestinal*: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, and weight loss. *Neurological*: ataxia, bradyphrenia, confusion, dizziness, fatigue, impaired attention and memory, nystagmus, speech disorder, and tremor. *Ophthalmological*: double vision. *Psychiatric*: agitation, anxiety, depression, insomnia, irritability, and labile affect. *Urological*: nephrolithiasis and UTI.

Serious—Dermatological: rarely, Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported. *Gastrointestinal*: cholecystitis, hepatocellular damage, and pancreatitis. *Haematological*: agranulocytosis, aplastic anaemia, sulphonamide reactions, and pancytopenia have been reported. *Immunological*: drug-induced hypersensitivity syndrome (DRESS/ Multi-Organ Hypersensitivity). *Musculoskeletal*: rhabdomyolysis has been reported. *Neurological*: coma, convulsions, myasthenic syndrome, NMS, and status epilepticus have been reported. *Ophthalmological:* Secondary rangle closure glaucoma. *Psychiatric*: psychosis and suicidal ideation. *Urological*: rarely hydronephrosis and renal failure.

Contraindications

- *Absolute*: hypersensitivity to the sulfonamides, zonisamide, or any of its excipients, and severe hepatic impairment.
- *Relative*: caution is recommended in those predisposed to urinary calculi or with co-prescribed medications that can contribute to metabolic acidosis.
- *Mild to moderate hepatic impairment:* doses should be increased more slowly, every 2 weeks, rather than weekly, and lower maintenance doses may be required. *Renal impairment:* doses should be increased more slowly, every 2 weeks, rather than weekly, and the medication discontinued if there is a clinically significant deterioration in the eGFR. Doses may need to be lowered in progressively worsening renal impairment.

Use in special populations

- *Elderly*: as a result of an age-related reduction in hepatic and renal function, the elderly are more commonly predisposed to side effects, particularly urinary calculi and dehydration, and lower doses are advised.
- *Pregnancy*: animal studies have demonstrated teratogenic effects; however, there are no studies in humans. There is no information available as to possible changes in pharmacokinetics during pregnancy. Monitor newborns for signs of metabolic acidosis. Use in pregnancy involves weighing up the potential benefits and side effects.
- *Lactation*: zonisamide is present in breast milk. Breastfed infants will have plasma levels equivalent to that of their mother, but infant serum levels decrease during the first month. The manufacturer's advice is to avoid breastfeeding for the duration of treatment and for 4 weeks after treatment has ceased. If breastfeeding continues, monitor the infant for drowsiness, developmental delay, and inadequate weight gain. Some clinicians recommend only partially breastfeeding to minimize exposure. There are no adverse effects reported in infants, but data is limited.

Efficacy

Epilepsy: Three RCTs of zonisamide used as an adjunct in focal-onset epilepsy in subjects already receiving 1–3 ASMs demonstrated a >50% reduction in seizure frequency in 28–42% of participants vs. 12–22% with placebo. A large randomized, double-blind, parallel-group trial demonstrated that zonisamide monotherapy was non-inferior to carbamazepine in the treatment of newly diagnosed focal-onset epilepsy.

PD: 2 RCTs in subjects (n = enrolled/completed, 422/354 and 196/166) with advanced-PD have shown significant reduction in 'OFF' time and UPDRS II and III scores at 25 mg and 50 mg, with a higher percentage of responders in the 50 mg arm.

Myoclonus-dystonia: A placebo-controlled, randomized cross-over trial (n = 24) found improved action myoclonus and disability (50 mg increased to 300 mg/day).

Dosing and monitoring

Dosing

- *For the treatment of epilepsy as an adjunct*: start treatment at 25 mg bd. This is increased after 1 week to 50 mg bd and then can be increased by 50 mg bd per week. The normal maintenance dose is 300–500 mg in two divided doses.
- *For the treatment of epilepsy as monotherapy*: start treatment at 100 mg od for a fortnight. Then increase to 200 mg/day for a fortnight, and then increase to 300 mg/day. The normal maintenance dose is 300 mg/day, although this can be increased by 100 mg in fortnightly intervals to 500 mg.
- *For the treatment of PD as adjunctive therapy*: 25–50 mg/day.

Monitoring

Consider serum bicarbonate monitoring for metabolic acidosis and undertake regular renal function testing.

Therapeutic drug monitoring Optimum seizure control, when used in monotherapy, occurs at plasma concentrations of 10–40 mg/L.

Pharmacokinetics and interactions

Pharmacokinetics

Oral bioavailability is >90%. T_{max} is 2–5 h. T_{max} may be prolonged, but total bioavailability is not affected, by food co-ingestion. 40–50% is protein-bound. Steady state is reached in 10–15 days. 65% of zonisamide is metabolized, primarily via CYP3A4 to 2-sulfamoylacetyl phenol which is subsequently glucuronidated. There is no autoinduction. The metabolites are inactive. Zonisamide, the unchanged drug (35%), and its metabolites are almost entirely eliminated by the renal system. The half-life varies, depending on the presence of enzyme-inducing ASMs. The half-life is ~50–70 h without co-prescribed enzyme inducers, and 25–35 h with co-prescribed enzyme inducers.

Interactions

See Table 24.76.

Table 24.76 Interactions of zonisamide

Medications which alter zonisamide plasma levels	Medications whose plasma levels are altered by zonisamide	Pharmacodynamic interactions
Levels decreased: carbamazepine, phenobarbital, phenytoin, primidone, and risperidone	Levels increased: carbamazepine–epoxide metabolite of carbamazepine	With other carbonic anhydrase inhibitors and bicarbonate: increased risk of renal calculi formation With CNS depressants, e.g. alcohol and MAOIs: increased risk of sedation

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